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A CRITICAL ANALYSIS OF TWENTY-ONE YEARS' EXPERIENCE WITH CÆSAREAN SECTION

By J. Whitridge Williams *

From February 1, 1899, until the end of December, 1920, 183 Cæsarean sections were done in the Obstetrical Department of The Johns Hopkins Hospital, and I have thought that it might be interesting to follow the evolution of the operation in our service, and to learn our point of view concerning certain of its various aspects.

Frequency

The 183 operations were done upon 145 women, 104 of whom had their first and only section in the service, while 41 others had one or more subsequent sections, as follows:

104 women had the first and only section in the service	104
8 women had the first section elsewhere and the second in the service	8
26 women had two sections in the service	52
2 women had the first section elsewhere and two in the service	4
5 women had three sections in the service	15
145	183

Of the entire number of operations, 122 were done by me and 61 by a succession of 13 residents. Accordingly, the results obtained are composite in character, and do not represent the experience of a single, and possibly peculiarly skillful, individual.

As the 183 sections occurred in a series of approximately 20,000 deliveries, their incidence was somewhat under 1 per cent. As will be shown below, 144 of them were done on account of disproportion between the size of the child and the pelvis, and I believe that great conservatism was observed in the indications for its performance. Quite one-half of our material consists of colored women, and as the incidence of contracted pelvis is 35 and 8 per cent in the two races, respectively, this means that approximately 3500 contracted pelves were observed in our black and 800 in our white patients, or a total of over 4000 in the series. Dividing that number by 144 shows that during a period of 21 years approximately one Cæsarean section was done in every 30 contracted pelves. As time has gone on, our indications have become somewhat more liberal, as is shown by the fact that only 50 sections were performed during the first 12 years of the period, as compared with 133 during the last 9 years—an average incidence of 4 and 15 sections per year, respectively.

The comparatively infrequent resort to Cæsarean section during the former period is in part accounted for by the fact that between the years 1906 and 1915 we gave pubiotomy an extensive trial. Forty-three such operations were done and

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all of the patients recovered; and, as will appear later, pubiotomy, at that time at least, constituted a very conservative procedure, no matter what one may now think of its justifiability and applicability. That many of these patients would otherwise have been delivered by Cæsarean section is shown by the fact that 11 patients in the present series had been subjected to one or more pubiotomies before Cæsarean section was resorted to, and that three of them required two and one three sections afterwards.

One of the striking features brought out by the consideration of our series of sections is that blacks require radical interference much more frequently than whites, our figures showing that Cæsarean section was performed upon 114 colored and 69 white women, with 57 and 14 repeated operations in the service, respectively—an incidence of 50 and 20 per cent. To particularize, it may be stated that 21 of the black women had two, and five had three repeated sections in the service; while none of the 7 white women had a third section in the service, although one of them (8955) had two sections following a previous section elsewhere, thus making three in all. It will be noted that these figures do not tally with those given at the beginning of the article, for the reason that they do not include 8 patients upon whom a second section was done in the service following a first one performed elsewhere.

Considering the types of operation performed, it is found that 121 were typical conservative sections, 4 extraperitoneal sections (Küstner), 1 postmortem section, and 57 supravaginal amputations of the uterus—the so-called Porro Cæsarean sections. It will be noted that no cervical Cæsarean sections were done. Of the 125 conservative and extraperitoneal sections 27 were repeaters, as compared with 21 in the 57 supravaginal amputations. Moreover, the comparatively frequent employment of supravaginal amputation of the uterus following the section should lend considerable interest to our analysis, and the reasons for its frequent utilization will be considered in some detail further on.

Mortality

Passing to the consideration of the mortality following Cæsarean section, it is found that 10 deaths followed the 183 operations, a gross mortality of 5.46 per cent; eight deaths occurring after the 126 conservative operations, and two after the 57 supravaginal amputations, or 6.35 per cent and 3.51 per cent, respectively. Before any deductions are made, it should be noted that the gross mortality following supravaginal amputation, which for purposes of brevity will hereafter be designated as the Porro operation, was about one-half of that following the conservative operation.

Careful study of our material has convinced me that a gross mortality of 5.46 per cent gives somewhat too sombre an idea of the dangers of Cæsarean section, and it will be seen that the deaths, which followed the operation in several instances, were in no way connected with it, and may be fairly deducted in determining the net mortality. For example, Case 4723, in which the patient with mitral stenosis and insufficiency was operated upon in the hope of preventing death from acute decompensation, made a good recovery from the operation, but died at home forty days later from the original heart lesion. Likewise, in Case 5709, the woman was suffering from broken compensation due to acute ulcerative endocarditis, and was operated upon as a last resort with a pulse of 136. She died on the eighth day, but autopsy showed that death had resulted from the original endocarditis and that no signs of wound infection were present. In Case 5911 the patient was an elderly primipara, who was admitted to the service with complete placenta prævia, a rigid cervix and advanced chronic nephritis. Death occurred on the eighth day following the section. Autopsy showed that it was due to the chronic nephritis; while negative cultures from the uterine and peritoneal cavities, as well as the absence of inflammatory lesions, demonstrated the absence of wound infection. Finally, in Case 6890, the patient was operated upon for eclampsia. Autopsy, 26 days after the section, showed that death had resulted from acute anemia following profuse gastric and intestinal hemorrhage, following the erosion of a duodenal ulcer.

Upon deducting these four deaths, which can fairly be claimed to have no connection with the operation itself, it follows that six deaths, which must be attributed to it, occurred after 179 Cæsarean sections—a corrected mortality of 3.35 per cent. Furthermore, it is interesting to note that the net mortality following the 121 conservative and 56 Porro operations presented variations similar to those observed in the gross mortality; as five deaths occurred after the former, as compared with one after the latter—a net mortality of 4.07 and 1.82 per cent for the two operations, respectively.

A good deal of light may be thrown upon the mortality, and the factors concerned in its production by considering our material from another point of view. Regarding the first 50 operations as representing the period of learning and the remainder as the period of more ripened experience, it is found that 6 deaths occurred in the first, as compared with 4 in the succeeding period—a gross mortality of 12 and 3 per cent, respectively. Upon deducting the four deaths, which were not primarily connected with the operation, it is found that five deaths occurred in the first 49 sections, as compared with one in the succeeding 130—a net mortality of 10 and 0.77 per cent, respectively. In other words, the net mortality was 13 times less than in the second period. Moreover, during the first period we performed 28 conservative and 22 Porro Cæsarean sections, with 5 deaths in the former and 1 in the latter, a gross mortality of 18.5 and 4.5 per cent, respectively. In other words, during the period of learning the mortality was four times greater after the former than after the latter operation.

Results

It should be noted that five of the 6 deaths directly attributable to the operation were due to general peritonitis, which resulted from the extension of infection through the uterine wound, while the sixth was due to the failure of an inexperienced resident to control hæmorrhage from the uterine artery during the course of a Porro operation. As the aseptic technique was, roughly speaking, identical throughout the entire

series, the question arises as to how the difference in the results during the two periods are to be explained, and why the mortality following the Porro operation was so much lower than after the conservative? To answer these questions, as well as to ascertain what other conclusions can be drawn from our experience, is the object of the present study.

The answer to the first question is perfectly clear, and consists in the fact that we now aim to operate before the onset of labor, or as soon afterwards as is feasible, upon patients who have not been examined vaginally for some days. During the period of learning, on the other hand, the significance of early operation was not appreciated, as it was currently taught that the ideal procedure was to allow the patient to go into the second stage, to subject her to the test of labor, and to complete delivery by Cæsarean section only after a tentative attempt with high forceps had failed to draw the head into the pelvic cavity.

This lesson was in great part learned by comparison between the results following the conservative and the Porro operations. The first supravaginal amputations were undertaken for the purpose of sterilizing the patient, usually at the second section, or occasionally at the first, if she urgently requested it, or when she was so deformed as to become a charge upon the community. We soon became impressed by the difference in the convalescence following the two operations, and during the period of learning noted that only 41 per cent of the patients subjected to the conservative operation had normal afebrile puerperia, as contrasted with 71 per cent after the Porro operation, not to mention the difference in mortality to which reference has already been made. Moreover, we gradually learned that patients upon whom conservative sections were done late in labor or following vaginal manipulations did badly, and sometimes died; whereas those in whom the uterus was amputated tended to have an ideal convalescence. This contrast was particularly noticeable when signs of intrapartum infection were present prior to operating.

The more favorable results following the Porro operation were at first attributed to the lessened resistance to infection of the incised involuting uterus, and seemed explicable in the same manner as the simple convalescence following the treatment of uterine myomata by supravaginal hysterectomy as compared with the more stormy one following myomectomy. Later, however, it was found that this was not the whole story; for when we came to examine microscopically uteri that had been amputated following Cæsarean section, particularly when the operation had been undertaken late in labor, it was noted in many instances that the decidua lining the lower uterine segment presented pronounced leukocytic infiltration and other signs of inflammation, which were usually lacking in the upper part of the uterus. Moreover, when such sections were treated with appropriate stains, streptococci and other bacteria could be demonstrated in the tissues. Such observations led us to conclude that the infection was due to an ascending process, which had not given rise to clinical symptoms at the time of operation. Thus, in 14 instances in which the uterus had been amputated late in labor, microscopic study conclusively demonstrated the existence of an ascending infection. In two instances the patients had presented signs of intrapartum infection, but in the other 12 the pulse and temperature were normal at the time of operation, and no signs were present which might lead one to suppose that infection had already occurred. The evidence thus adduced is so clear that it is now realized that whenever a considerable time has elapsed between the onset of labor and the performance of Cæsarean section, we must reckon with the probable existence of latent infection. In this event, it would appear that the involuting uterus is unable to offer a sufficient resistance to the spread of the infection, with the result that the process extends through the uterine incision to the peritoneum, giving rise to a general peritonitis to which the patient almost always succumbs. Since the probability of latent infection in prolonged labor has been recognized and our procedure modified accordingly, the results following conservative Cæsarean section have become highly satisfactory.

The difference between the two operations can be still further demonstrated by comparing the clinical course of the puerperium. Upon designating as febrile all patients in whom the temperature reaches 100.5° F. on one occasion or more, the convalescence was found to be afebrile in 43.9 and 59.6 per cent following the conservative and Porro sections, respectively. Furthermore, the comparison becomes even more striking when the cases are arranged in groups according as the operation was done before the beginning of labor or at varying periods after its onset.

TABLE I. SHOWING INCIDENCE OF NORMAL PUERPERIA ACCORDING TO TIME AT WHICH SECTION WAS DONE

	Conservative			Porro		
	Normal	Febrile	Per ct.	Normal	Febrile	Per ct.
Before onset of labor	25	21	54.4	10	4	71.4
1 to 6 hours after onset....	25	28	47.2	7	5	58.3
6 to 12 hours after onset...	1	6	14.3	1	0	100
12 to 24 hours after onset..	2	8	20	4	3	57.1
Over 24 hours after onset..	1	6	14.2	12	11	52.2
	54	69	43.9	34	23	59.6
	123			57		

This table shows that there was a progressive and rapid diminution in the number of afebrile puerperia according as conservative section was done before the onset of labor or after the lapse of 24 hours—54.4 per cent as compared with 14.2 per cent. After the Porro operation, on the other hand, it is noted that afebrile puerperia are much more frequent, and while their incidence tends to decrease as the operation is performed late, it is nevertheless practically the same when the Porro operation is done after 24 hours of labor as when the conservative section is done before the onset of labor. Such observations clearly indicate that the involuting uterus

represents a *locus minoris resistentiæ,* and that its removal does away with a considerable danger of infection.

The difference in results following early and late operation on the one hand, and the conservative and Porro operation on the other, can likewise be demonstrated by considering the mode of healing of the abdominal incision.

Upon arranging our cases in four groups according as the operation was done before labor, one to twelve hours after the onset of labor, late in labor, and after the appearance of clinical signs indicating the existence of intrapartum infection, respectively, (as in Table II), it is noted that following the conservative section there is a progressive increase in the incidence of stitch abscess and actual infection of the wound, which occur three times more frequently when the operation is done late in labor than at its onset. In the corresponding groups following the Porro section, no such change can be noted, and in the 48 operations comprised in the first three groups the incidence of defective wound healing was only 4.17 per cent as compared with 13.44 per cent following the conservative operation.

Moreover, when the patients were operated upon in the presence of intrapartum infection still more striking differences were noted. Thus, in the two instances in which the conservative operation was done, both patients died before the end of the first week and were not included in the table, while of the eight in which the operation was ended by amputation of the uterus none died, but in 37.5 per cent of them the convalescence was disturbed by widespread infection of the abdominal wound.

TABLE II. SHOWING HEALING OF ABDOMINAL WOUND ACCORDING TO TIME AT WHICH CÆSAREAN SECTION WAS DONE

Time of operation	Conservative							Porro						
	Cases	Ideal	Stitch abscess	Per cent	Infected wound	Per cent	Total defective wounds	Cases	Ideal	Stitch abscess	Per cent	Infected	Per cent	Total defective wounds
Before onset.....	45	41	3	6.67	1	2.2	8.9	13	12	0	0	1	7.6	7.6
1 to 12 hours.....	62	53	5	8.06	4	6.45	14.5	15	15	0	0	0	0	0
Late in labor	12	9	2	16.67	1	8.33	25.	20	19	1	5	0	0	5
Intrapart. infec...	..	..	..	..	..	..	..	8	5	0	0	3	37.5	37.5
Total	119	103	10	8.40	6	5.4	13.44	56	51	1	1.78	4	7.14	8.93

(Does not include 7 patients who died within week of operation—6 conservatives and one Porro.)

It cannot be stated precisely why defective wound healing occurs so much more frequently following the conservative operation at the several periods, although it may be assumed that latent infection is more probably present in patients operated upon late, and, if so, it may result in soiling and subsequent infection of the abdominal wound without causing a fatal peritonitis. In the presence of intrapartum infection, on the other hand, the patients usually die from infection following the conservative operation before local signs appear in the abdominal wound; whereas after the Porro operation the peritoneum is able to take care of the infecting agents in the absence of the involuting uterus, while localized infectious processes tend to develop in the abdominal wound.

We now turn to the consideration of the factors concerned in the causation of death following Cæsarean section. As reference has already been made to the four deaths which I do not believe should be attributed to the operation itself, six others remain for consideration. One of these occurred during the course of a Porro section, while the other five followed conservative sections. The first death (1548) was due to hæmorrhage, the patient succumbing on the table as the result of failure of an inexperienced resident to control the bleeding from one of the uterine arteries. The other five were due to infection. In two the fatal outcome was due to unavoidable accidents. Thus, in Case 4116, the patient, who had had two preceding pubiotomies, was operated upon at an appointed time before the onset of labor and died five days later from general peritonitis. Afterwards, it was found that owing to a defect in the autoclave all of the dressings had been imperfectly sterilized. In Case 8826, death after the third section was due to infection following the imperfect repair of a loop of bowel, which was adherent to the abdominal cicatrix and which was wounded when the abdomen was opened.

The other three deaths, on the other hand, were due to errors in judgment and, with our present knowledge, should have been avoided. Thus, in Case 1256, a conservative section was done late in labor upon a patient with normal pulse and temperature. In Case 1611 a repeated conservative section was done 12 hours after the onset of labor upon a patient who presented signs of intrapartum infection with a temperature of 100.8°; and finally, in Case 2158, the patient was given a test of labor in the second stage and had a pulse of 116 and a temperature of 101° when operated upon.

Pelvic Indications

As has already been mentioned, 144 of the 183 sections were done an account of disproportion between the size of the child and the pelvis, while the other 39 were necessitated by non-pelvic indications, an incidence of 78 and 22 per cent, respectively.

Table III gives an idea of the various indications, and illustrates very clearly the great differences which prevail in white and colored patients, as seen in Baltimore, the pelvic indication being present in somewhat less than six-tenths of the former, as contrasted with nine-tenths of the latter. Furthermore, it is seen that in the colored women the various types of rhachitic pelvis afforded the predominant indication, as they made up 98 of the 103 contracted pelves requiring Cæsarean section in that race; while in the white women, on the other hand, only 10 of the 41 abnormal pelves were rhachitic in origin. Or, taking the entire number of sections into consideration, rhachitic pelves offered the indication for 86 per cent of the operations in the blacks as compared with 14.5 per cent in the whites. Consequently, if the application of suitable dietetic and hygienic measures should eventually lead to the

disappearance of rickets, Cæsarean section would be very rarely indicated in the black race.

In the whites, on the other hand, the most usual pelvic indication was afforded by the simple flat pelvis, which was

TABLE III. SHOWING INDICATIONS FOR 183 CÆSAREAN SECTIONS

Pelvic indications				Other indications			
Type of pelvis	Total	White	Black	Condition	Total	White	Black
Generally contracted rhachitic.	86	3	83	Eclampsia	9	5	4
Simple flat	15	15	..	Heart	8	6	2
Flat rhachitic	13	6	7	Atresia of cervix	4	4	..
Scolio-rhachitic	8	1	7	Ovarian cysts	3	3	..
Kypho-scolio-rhachitic.	1	..	1	Neglected transverse	3	3	..
Generally contracted.	6	4	2	Premature separation of placenta.	2	1	1
Funnel	6	5	1	Nephritic toxæmia	2	2	..
Achondroplasic	4	4	..	Myoma	1	..	1
Kyphotic funnel	2	1	1	Ventral fixation	1	1	..
Coxalgic	1	..	1	Pregnancy in rudimentary horn.	1	..	1
Hypoplastic dwarf	1	1	..	Hour-glass contraction.	1	..	1
Oblique (luxation)	1	1	..	Placenta prævia	1	1	..
				Excessive size of child.	1	1	..
				Carcinoma of cervix.	1	1	..
	144	41	103		39	28	11
			144				39

noted in 15 instances; while not a single pelvis of that type necessitated interference in colored women. Indeed, the simple flat pelvis is the most important variety of pelvic contraction in white women, as it frequently happens that such pelves presenting so relatively long a diagonal conjugate as 10 to 10.5 cm. sometimes give rise to serious dystocia and lead to the birth of a number of dead children before the patient comes into the hands of a competent obstetrician. Furthermore, it is interesting to note that the various types of contracted pelvis, due to factors other than rickets, were observed much more commonly in the white women, notably the generally contracted, funnel, and chondrodystrophic pelves.

NON-PELVIC INDICATIONS

Passing to the non-pelvic conditions, it will be seen that eclampsia offered the indication for section in 9 instances, and was of approximately equal frequency in the two races. This is neither the time nor the place to consider the justifiability of the treatment of eclampsia by this means, although I may say briefly that it is exactly in connection with this indication that the operation is being greatly abused, and that I expect to employ it much less frequently in the future than I have in the past. With my present experience I hold that Cæsarean section is indicated in the treatment of eclampsia only when the cervix is rigid and undilated and the patient has failed to show any improvement after venesection.

The next most common indication was afforded by heart disease, which was present in eight instances—in six whites and two blacks. In each instance the patients were suffering from marked decompensation, which had failed to yield to medicinal treatment, so that the operation was undertaken as a last resort and in the hope that by avoiding the strain of the second stage of labor the life of the patient might be preserved. As in most of these cases the lesion was a mitral stenosis, which might be expected to become worse with succeeding pregnancies, it was felt that such a possibility should be obviated by a sterilizing procedure, and consequently the operation was usually terminated by amputation of the uterus or by some operation upon the tubes.

The mere enumeration of the other non-pelvic indications in the table suffices to indicate that they were of such character as not to require extended comment, except in the case of the three sections for neglected transverse presentations and the one for placenta prævia. Generally speaking, it may be said that Cæsarean section is not indicated in the former condition unless such a degree of pelvic deformity is present as to render version and extraction out of the question. In the three cases here mentioned, however, quite different conditions obtained. In each instance the patient was a multipara with a normal pelvis who had previously had a number of normal spontaneous labors, but who had been so neglected that after a long labor she had been admitted to the service with an arm protruding from the vulva, the uterus tetanically contracted, but with the child in excellent condition. Under such circumstances version and extraction were out of the question, and the alternative lay between decapitation of the live child and Cæsarean section. Furthermore, owing to the fact that the patients had been repeatedly examined by ignorant physicians or midwives, it was felt that the probability of infection was so great that if a section were done the uterus must be sacrificed. Accordingly in each instance a Porro Cæsarean section was performed and the patient made an uninterrupted recovery.

The single case of placenta prævia also deserves mention, especially as the patient is the only one in my experience who has seemed to justify the employment of Cæsarean section in connection with this complication. Of course, I have realized for years that in rare instances, when the cervix is rigid and undilated and the bleeding profuse, Cæsarean section will offer the most favorable prospect for safe delivery in complete placenta prævia. The rarity of such a combination of circumstances is shown by the fact that in the 66 cases of placenta prævia observed in the service, this was the only one in which Cæsarean section appeared indicated, and strange to say, the death which followed it constitutes one of the few fatalities associated with that complication. In this instance the patient was a very anæmic elderly primipara with advanced chronic nephritis, and, as has already been indi-

cated, died on the eighth day following the operation, the autopsy showing that death had resulted from the underlying chronic nephritis rather than from infection or loss of blood.

Generally speaking, I believe that Cæsarean section should play only a very minor part in the treatment of placenta prævia in the hands of competent obstetricians, and I contend that the use of the rubber bag will give almost ideal results. That this has been the case in our hands, is shown by the fact that only one maternal death occurred in the last 40 cases treated by that method.

Porro Cæsarean Section

Reverting to the consideration of the Porro Cæsarean section, it will be noticed that the operation has been employed relatively frequently, and constitutes nearly one-third of our total number of sections (57 out of 183). Its frequent utilization has been in great part due to one of two factors. First, that it has been followed by uniformly good results, particularly in the presence of manifest or latent infection, and second, that we have regarded it as the most efficient and safest means of effecting sterilization, more particularly as a large number of our patients are colored women of relatively low intelligence in whom we have felt that an unlimited number of repeated Cæsarean sections was not justifiable.

In considering the 57 Porro sections in greater detail, it is found that in 36 instances the uterus was removed as a primary procedure following the delivery of the child, while in 21 it was removed at a second or third Cæsarean section. The following table gives the indications for the primary operations:

	Cases
Late second stage, or manifest intrapartum infection	9
Sterilization	6
Heart disease	5
Atresia of cervix	4
Transverse presentation	3
Uncontrollable hæmorrhage	2
Rupture of uterus in service	2
Dystocia following ventral fixation	1
Pregnancy in rudimentary horn of uterus	1
Hour-glass contraction of uterus	1
Myoma of cervix	1
Apoplexy of uterus incident to premature separation of placenta	1
Total	36

I shall discuss each group as briefly as possible. In view of what has already been said, the nine cases in which the operation was performed late in the second stage of labor need little consideration, as it has already been demonstrated that in such circumstances the operation may be regarded as a life-saver. Seven of the nine uteri in this group were examined microscopically after amputation, and four of them presented positive evidence of ascending infection, so that, had the uterus been retained, the probabilities are that many of the patients would have died from infection by the end of the first week.

In the six instances in which the uterus was removed for the purpose of sterilizing the patient, the indication was offered either by the direct request of the patient or by the existence of such deformity or so low a grade of intelligence that I felt that it was a service to the state to prevent further pregnancies.

Serious cardiac decompensation was the indication for five operations (5709, 5773, 6753, 7705 and 7832). In each instance the condition of the patient was so serious that the operation was undertaken from a double point of view: first, to carry her over the present emergency, and second, to prevent the exacerbation which must inevitably occur in future pregnancies.

In four instances (1788, 2757, 5381 and 6801) the indication for amputation of the uterus was afforded by pronounced atresia of the cervix. In three patients the condition had followed gynecological operations upon the cervix which had been performed elsewhere, while in the remaining patient no clue to the etiology of the condition could be elicited. In each instance there was no visible opening in the cervical region, which might serve as a basis for a vaginal operation, but the main indication for the radical procedure was afforded by the fact that all of the women presented signs of intrauterine infection upon admission to the service, which was afterwards confirmed by histological examination, so that it was felt that a conservative section would have seriously compromised the chances of recovery.

The three cases of neglected transverse presentation, in which the uterus was amputated in preference to decapitating a live child, have already been considered and call for no further comment (5238, 5418, 6708).

In two instances the uterus was removed on account of atony which did not yield to the ordinary methods of treatment (5051, 7072). In both patients it was intended to do a conservative section, and the uterine incision was closed in the usual manner in spite of more than the usual amount of bleeding. The uterus, however, remained so flabby and atonic, notwithstanding several injections of pituitrin and ergot, as well as vigorous mechanical stimulation, that it was felt imperative to remove it. In a third patient the uterus was amputated on account of the hæmorrhagic disassociation of the uterine muscle following premature separation of the normally implanted placenta (7190). In this instance the uterus absolutely failed to contract and presented the consistency of wet chamois-skin, so that we were compelled to remove it from the primiparous patient after all the sutures had been laid.

It will be noted that we have classed as Porro sections two cases in which intrapartum rupture of the uterus occurred in the service, and in which immediate operation was performed (6838 and 7692). In one of these rupture occurred five hours after the onset of labor in a secundipara with a slightly contracted pelvis, whose previous labor had ended spontaneously. The second rupture resulted from the impaction of an ovarian cyst in the pelvic cavity in a multiparous woman. In both instances the uterine wounds were so exten-

sive and complicated that amputation of the uterus seemed to afford the most appropriate means of meeting the situation. The two cases in which the uterus was amputated on account of a full-term pregnancy in the rudimentary horn of a bicornate uterus (2822), and on account of a large myoma of the cervix, which completely blocked the pelvic canal and rendered spontaneous labor impossible (6384), need no justification.

In another instance the uterus was removed in order to overcome the dystocia resulting from ventral fixation (Case 2479). This patient had a normal pelvis and had previously given birth spontaneously. The existence of dystocia was not recognized until late in labor, when examination showed that the anterior wall of the uterus had become "buckled" in such a manner as to prevent engagement of the head, while at the same time the uterine cavity had become divided into two compartments, the anterior of which was occupied by the feet of the child, which were in such a position as to be just beyond the reach of the hand of the operator so that version could not be effected. The uterus was amputated, on account of the extensive manipulation, and microscopic examination demonstrated that it was a wise decision, inasmuch as definite evidences of ascending infection existed.

The last primary Porro Cæsarean was indicated by the rare condition of hour-glass contraction of the uterus (Case 10840). In this instance a bag had been introduced for the purpose of inducing labor in a patient who had gone some days beyond term. After its expulsion, labor came to a standstill, and signs of intrapartum infection developed. The half dilated cervix presented swollen and œdematous margins, so that prompt delivery seemed indicated. The resident obstetrician introduced his hand into the uterus with the intention of completing manually the cervical dilatation, but found that the contraction ring was so tightly clamped about the neck of the child that it seemed unlikely that it could be delivered even after the cervix had been dilated. In view of these conditions, Cæsarean section seemed imperative, and on account of the existing infection, as well as the extensive manipulation to which the patient had been subjected, removal of the uterus appeared to be the only procedure justifiable. A live child was obtained and the patient made an ideal recovery.

The following list gives an idea of the indications for the Porro operation in the 21 cases in which the uterus was amputated at a repeated section:

	Cases
Late second stage	4
Sterilization	11
Impetuosity of operator	1
Tearing of uterine incision	1
Rupture of scar of previous section	1
Fear of rupture of scar of previous section	1
Extensive raw area up on anterior wall of uterus	1
Blocking of vulva by condylomata	1
Total	21

These cases can be disposed of briefly. In the first group, the operation was fully justified by the microscopic demonstration of an ascending infection in each of the amputated uteri. Of the 11 cases in which sterilization was the indication for the operation, the histories show that in seven the uterus was amputated at the repeated section at the direct request of the patient; while in the other four sterilization was effected at the third section upon my own initiative, as I felt that women who have had three sections had fulfilled their reasonable duty to the state.

In the case designated as "impetuosity of operator" (1548), the uterus was amputated by a former resident during my absence. The operation was performed before the onset of labor, and a small child was delivered, which might have been born spontaneously. It is interesting to note that this is the case in which the patient died from hæmorrhage on the operating table, and represents the only death in the entire series attributable to the Porro operation.

In Case 6939 the indication for removing the uterus at the second section was accidental, as we had expected to do a conservative section, but in extracting the child the lower end of the uterine incision tore downward beneath the peritoneum of the broad ligament, and so complicated a wound resulted that it seemed more conservative to remove the uterus than to attempt to repair it.

In Case 7570 the uterus was removed on account of rupture of the scar of the previous section during the eighth month of pregnancy. The details of this accident will be described by Thomas O. Gamble in an article on the "Behavior of the Uterine Cicatrix following Cæsarean section" which will shortly appear, and is of interest from two points of view—first, that it is the only occurrence of the kind in 48 women upon whom repeated sections have been done in the service, as well as in 12 other women who were delivered by the natural passages subsequent to a preceding section, and secondly, on account of the comparatively trifling symptoms associated with the accident.

In Case 8697 the uterus was removed through an excess of caution, but also at the expressed desire of the patient. In this instance infection followed the first section, which had been done elsewhere, and resulted in the formation of an extensive utero-abdominal fistula. This was eventually repaired, and necessitated an extensive resection of the uterine wall which was closed with silk sutures. The patient soon afterwards became pregnant and came to us for a second section at which we amputated the uterus with the idea that the cicatrix of the former operation might be a source of danger in future pregnancies, but when the specimen was examined microscopically no trace of the cicatrix could be found, except a fine linear scar upon its anterior wall. This specimen also will be described by Dr. Gamble.

In another instance (10758) the indication for operation was afforded by the fact that following the first section such intimate and extensive adhesions had developed between the uterine wall and the intestines that, after they had been freed, a raw area the size of the palm of one's hand remained upon the anterior surface of the uterus. As it could not be covered with peritoneum, it was felt that still more extensive adhe-

sions would result if the uterus were retained, and consequently it was amputated.

Finally, in the last case of the series (9323) the uterus was removed on account of fear of infection at the second section. In this instance the vulva was entirely occluded by large condylomatous masses bathed by purulent secretion, and it was felt that the chances of infection would be excessive if the uterus were retained.

Upon considering these various indications in a critical spirit, it may be admitted that we have perhaps employed the radical operation too freely as a means of effecting sterilization, and within the last few years we have attempted to restrict its employment for that purpose by resecting the tubes and retaining the uterus. We now ask women who request sterilization, or whom we feel should be sterilized, whether they wish to continue to menstruate or not after the last section. It they reply in the affirmative, sterilization is effected by doubly ligating the tubes and burying their uterine ends between the folds of the corresponding broad ligament; but, if they reply in the negative, I still continue to remove the uterus as the safest and most efficient method of relieving the existing situation and of effecting definitive sterility.

Possibly, a similar criticism may be made concerning certain of the cases in which the patient was sterilized on account of broken compensation. It may, however, be stated that in such cases haste is imperative, and we are able to amputate the uterus in a shorter time than is required for a conservative Cæsarean section followed by a sterilizing operation upon the tubes. Likewise, certain of the operations which were done for some of the less common indications may be open to criticism, but each such case must be judged upon its own merits, and the justifiability of the procedure must depend upon the personal judgment and experience of the operator. In general I feel, notwithstanding certain very manifest limitations, that the Porro Cæsarean section still remains the safest means of delivering the patient, and I must confess that I perform it whenever a suitable opportunity presents. It should, however, be realized that its prime indication is when Cæsarean section is required late in labor and particularly when signs of intrapartum infection are present. In such circumstances, it is universally admitted that the mortality following the typical conservative section is too high for it to be considered a justifiable procedure, and we then have to decide whether it is better to remove the uterus and thereby do away with the possibility of future pregnancies, or to perform craniotomy upon a live child. Doubtless, such a problem will be approached differently according to one's own experience and predilections, and it must be admitted that in the future such a choice may not be necessary, particularly if the claims of the advocates of the several varieties of so-called extra-peritoneal Cæsarean section are borne out; but, until they are, I shall continue to do the Porro operation in the type of cases under consideration. From my experience with the typical extraperitoneal Cæsarean section, I should certainly hesitate to resort to that complicated procedure in any instance in which the patient is presumably already infected, as I cannot conceive of more favorable conditions for the spread of infection than the extensive broad ligament wounds which are made in the course of that operation.

Evisceration of the Uterus

In studying critically the convalescence following our series of Cæsarean sections, a number of factors have been encountered which may influence its course. The first which may be mentioned is the effect upon the course of the puerperium of the old practice of eviscerating the uterus before incising it. It will be recalled that during evolution of the modern Cæsarean section the possibility of severe, or even fatal, hæmorrhage from the incised uterus was constantly in mind. For this reason it was originally the practice to attempt to control hæmorrhage by applying a constricting rubber ligature about the cervix before opening the uterus. This, of course, necessitated eviscerating the undelivered organ through a long abdominal incision. After experience had taught that the application of the ligature was not necessary, the practice of eviscerating the uterus was continued for a time so that an assistant could compress the lower segment manually, and thereby control the flow of blood through the uterine arteries when necessary.

Upon studying the histories of our patients we find that the uterus was eviscerated in 26 conservative sections prior to 1911. After that date a smaller abdominal incision was made, and the uterus was incised *in situ* and not delivered until after the child had been extracted. Upon comparing the convalescence following the two procedures, it was found that the puerperium was afebrile in 31.8 per cent of the former as compared with 51.6 per cent of the latter. Whether evisceration of the uterus ever led to the death of a patient it is impossible to state, but it is readily understood how it favored the possibility of infection, as the bulky unemptied uterus inevitably came into intimate contact with the external abdominal wall, and was likewise handled more extensively than when it is incised *in situ*. At present we eviscerate the uterus only in patients showing signs of intrapartum infection in whom the organ is to be amputated after the delivery of the child. In such cases the abdominal wound is brought together by clamps above the cervix, and by the use of gauze packs the peritoneal cavity is still further protected against contamination by the infected liquor amnii.

Since abandoning the practice of evisceration a much smaller abdominal incision has been necessary, and I usually prefer to make it below the umbilicus. My preference for this low incision, rather than for the high one advocated by Asa B. Davis or for one extending midway above and below the umbilicus as advocated by others, is that it is sufficiently large for the extraction of the child, and at the same time permits accurate exploration of the pelvic contents, as well as amputation of the uterus should an unexpected necessity for a radical operation arise. Whereas, with the high and mid-umbilical incisions the abdominal wound must be extended downward before the pelvic contents become accessible.

SUTURE OF UTERINE INCISION

Passing to the method of suturing the uterine incision, it is found that considerable divergence in practice prevailed during the early and later periods of the series. In the early cases the uterine incision was closed with deep, interrupted silk sutures, which passed down to but did not include the decidua. After a while we began to use fine interrupted silk sutures between the deep sutures, in order to secure better approximation of the peritoneal layer; a little later catgut was substituted for silk, and finally, the method was evolved which is now employed. For years we have laid the greatest stress upon the manner in which the uterus is sutured and are well satisfied with the following procedure: As many deep interrupted chromic catgut sutures as necessary are laid. These extend through the bulk of the muscle, but do not include its superficial layer or the peritoneal covering. If, after they are tied and cut, there is any gaping of the muscle between the sutures, a continuous catgut suture brings together the gaping points; and finally, the peritoneum and superficial muscle are brought together with a single continuous catgut suture, which completely buries the knots of the deep sutures and brings the peritoneal edges into the closest approximation.

Our records show that the uterine incision was closed with silk in 20 and with catgut in 106 conservative sections. As with but few exceptions, silk sutures were employed at the same time as evisceration was practised, it is impossible to draw definite conclusions as to whether the employment of the former had any influence upon the course of the puerperium, or whether the comparatively poor results obtained at that time was associated with the evisceration of the organ, and particularly with the selection of patients for operation.

RUPTURE OF CICATRIX IN SUBSEQUENT PREGNANCY

Closely allied with the question of suturing the uterus is the consideration of how the resulting scar will stand the distention incident to subsequent pregnancies. A voluminous literature has accumulated upon the subject, and it is generally believed that the scar yields in from 3 to 5 per cent of subsequent pregnancies, when the uterine contents are extruded into the abdominal cavity with the result that the child is inevitably lost and the mother perishes from infection or hæmorrhage unless promptly operated upon. Of course, this accident depends in part upon the manner in which the uterus was orginally sutured, and particularly whether its healing was complicated by infection. The possibility of its occurrence has been so emphasized that the dictum "once a Cæsarean, always a Cæsarean" has obtained very general acceptance. In our experience, however, the danger of subsequent rupture has proved to be less than is generally believed, and we attribute its relatively infrequent occurrence to the care with which we have closed the uterine incision. Rupture occurred but once in 48 women who had repeated sections in the service, as well as in 12 others who were delivered by the natural passages following a previous section.

An interesting point in this connection is that in many of the repeated sections no trace of the cicatrix of the previous section could be noted on inspecting the unopened uterus at the second or third operation; while in other instances the only evidence of it consisted in adhesions over the anterior surface of the uterus, which apparently involved the old scar. So far as I can recall, with the exception of the actual case of rupture, signs of stretching of the cicatrix were noted in only a single uterus before it was incised at the subsequent section. On the other hand, when we came to study the conditions obtaining in the 21 uteri which were amputated at a final section, we found a varying condition of affairs. In many instances no trace of the cicatrix could be observed; in others the site of the previous incision was marked by a shallow depression upon the inner or outer surface of the uterus; while in a still smaller number a longitudinal depression upon both its outer and inner surfaces marked its site, and had led to a greater thinning of the uterine wall there than elsewhere. Microscopic examination, however, showed that, irrespective of the gross appearance of the cicatrix, no trace of scar tissue remained, and that the muscle fibers crossed the site of the original incision as if it had never been made. I shall not enter into details concerning this subject, for the reason that my assistant, Dr. Thomas O. Gamble, is now engaged in an extended study of all of its phases.

SITE OF PLACENTAL IMPLANTATION

Many writers upon Cæsarean section advise that every effort should be made to locate the situation of the placenta in order that the uterine incision may be made in such a location as not to involve it. Although for years we have made it a rule to attempt to locate before operation the situation of the placenta by determining the course of the round ligaments, and still continue to do so as a matter of diagnostic interest, we make no attempt to avoid the placental site, and as a matter of routine incise the uterus in the midline of the lower part of its anterior wall, except in the rare instances in which it is so pendulous that its posterior wall lies in contact with the anterior abdominal wall.

At the same time, figures concerning the location of the placenta may be of interest, and analysis of the notes which were available in 157 operations gives the following results: posterior implantation, 94, anterior implantation, 62, placenta prævia, 1. In other words, anterior implantation was observed in 38 per cent of the cases; and, consequently, if the anterior wall be incised as a matter of routine, the placenta will be involved in two cases out of five.

As has been indicated above, we regard this as a matter of indifference, so that when the placenta lies anteriorly we cut through it and deliver the child through the wound, and the only difference which we have noted is that in such cases there is a profuse preliminary gush of blood, which ceases as soon as the child is extracted and the uterus begins to retract. So far as the convalescence is concerned, our notes show no difference between the cases in which the placenta was incised and those in which it was not.

Use of Pituitary Extract

For many years it was our habit, as soon as the abdominal wall was incised, but before opening the uterus, to inject two barrels of ergotol into the arm or thigh of the patient for the purpose of stimulating the retraction of the uterus and thus preventing bleeding. When pituitary extract came into use we employed it in preference to ergotol. In several instances, however, in which it was necessary to free dense adhesions the action of the drug became manifest before we were ready to incise the uterus, with the result that it became tetanically contracted, and seemed to interfere with the placental function. While this had no serious consequences, we thought it safer to defer employing it until the uterus had been incised, and we then developed the custom of injecting 2 c. c. directly into the uterine substance whenever the uterus did not contract satisfactorily or if the hæmorrhage were excessive. Thus far no deleterious effects have been observed, but in view of the fact that apparently aseptic abscesses sometimes follow the injection of pituitary extract into the muscles of the thigh, it must be assumed that sooner or later such an accident will happen when it is injected into the uterus, when, of course, its consequences may be serious. For this reason we have recently abandoned the practice and now inject the medicament into the muscles of the thigh as a routine procedure as soon as we are ready to incise the uterus.

Condition of Child

It is usually stated that the Cæsarean section child is born in an apnœic condition and sometimes is deeply asphyxiated. This is believed to be due in part to the transmission of the anæsthetic agent through the placental circulation, and in part to the lack of friction which is normally associated with birth through the natural passages. Upon analyzing our histories I was surprised to find that such conditions were encountered less frequently than is ordinarily stated, and from the 145 histories which contained notes concerning the establishment of respiration in the child, we have collected the following figures:

Cried at once	75 cases	(51.7%)
Slightly asphyxiated	60 "	(41.4%)
Deeply asphyxiated	10 "	(6.9%)

In 16 other cases the child was born dead, but in no instance could its death be attributed to the operation, as in all such cases the section was undertaken for the sake of the mother and quite irrespective of the condition of the child. Consequently, it appears permissible to conclude that if the child is alive and in good condition when the operation is begun, it will be born alive, after which its chances for prolonged life will be the same as after normal delivery.

Formation of Adhesions

Another point in connection with the convalescence from Cæsarean section is the occurrence of adhesions between the uterine wound and other structures. In the old days, before aseptic technique had been developed and when the retraction of the uterus was relied upon to check hæmorrhage without the application of sutures, the formation of dense adhesions between the uterus and anterior abdominal wall was the rule. At that time this was so much the case that one expected in subsequent operations to deliver the child through a utero-abdominal fistula without opening the peritoneum.

So far as I can ascertain, no figures are available concerning the incidence of such adhesions following the modern technique, and although it is often possible by examination of the living woman to determine their existence, no accurate statement can be made as to their frequency. On the other hand, when repeated sections are done, definite conclusions can be drawn by noting the condition of affairs at the time of operation. Thus, upon analyzing the 48 such cases in our series we find the following:

	Cases
No note	2
No adhesions	12
Slight adhesions	10
Omental adhesions only	6
Broad adhesions	7
Dense adhesions	11

In other words, adhesions were absent in one-fourth, while broad or dense adhesions were present in one-third of the cases.

It is interesting to attempt to determine what relation, if any, the character of the convalescence bears to their formation, and whether a febrile puerperium favors their development. As in 10 instances the preceding section was done elsewhere, it is impossible to make any statement concerning the convalescence following it; but in 37 cases we have notes concerning the previous convalescence and the accompanying table summarizes the findings:

	Convalescence, Normal	Febrile
No adhesions	4	7
Slight adhesions	3	7
Omental adhesions	2	3
Broad adhesions	3	2
Dense adhesions	2	4
	14	23

In other words, the puerperium was normal in 38 and febrile in 62 per cent of the cases, and adhesions of the various types occurred after each, but were nearly twice as frequent after a febrile convalescence. It is, therefore, apparent that while a febrile puerperium appears to favor their formation, an afebrile puerperium does not necessarily insure their absence.

This being the case, it seems justifiable to infer that the occurrence of adhesions is not always the result of actual infection, but may quite as well be associated with the presence of raw surfaces resulting from defective methods of suturing the uterus, or from other traumatic factors. Such a conclusion is only hypothetical, but a certain degree of probability is lent to it upon considering the differences observed according as the first section was done elsewhere or in our service, as it may be assumed that it is possible that other operators sutured the uterus less carefully than we. Thus, broad or dense adhesions were noted in seven out of the nine

operations done elsewhere, as compared with 11 in the 37 cases done here. In other words marked adhesions developed in 76 and 30 per cent of the two groups respectively.

CORPUS LUTEUM AND SEX OF CHILD

From the time of Hippocrates to Rumley Dawson, many writers have believed that boys are derived from ova originating in the right and girls from those in the left ovary. Since our attention had been directed to this point, we have made it a practice at Cæsarean section to examine the ovaries carefully, and to note whether the corpus luteum was visible, and, if so, in which ovary it was situated. Notes to that effect were made at 99 operations, and upon analyzing them it was found that no corpus luteum was discoverable in one-third of the cases, while it was present in the other two-thirds.

When the corpus luteum was present in the right ovary 23 boys and 13 girls were noted, as compared with 16 boys and 12 girls when it was situated in the left ovary. In other words, in our experience, more boys than girls were obtained, irrespective of whether the corpus luteum was in the right or in the left ovary, and thus convincing evidence is adduced against the correctness of the theory that boys are derived from one and girls from the other ovary.

An interesting point in connection with these figures is that they demonstrate very clearly the fallacy of attempting to draw conclusions from too small a number of cases. For example, in the 64 cases in which the corpus luteum was present and the sex of the child was noted there were 25 girls and 39 boys, a ratio of 100 to 158, as compared with the normal of 100 to 106. With such figures at hand, an incautious person might be tempted to draw various erroneous conclusions, as for example that the existence of contracted pelvis or of some other condition which necessitates Cæsarean section may lead to a predominance of boys. That such a conclusion is unjustifiable, is shown by the fact that when the entire number of sections was considered the ratio of girls to boys was 100 to 107, which closely approaches the normal, and indicates that the former abnormal ratio was entirely accidental and of no particular significance.

CONCLUSIONS

1. This analysis is based upon 183 Cæsarean sections performed upon 145 women up to December 31, 1920.

2. The operations were done in a series of approximately 20,000 deliveries, and comprise 104 single, and 79 repeated sections. The latter were done upon 41 women, 34 of whom had two, and 7 three sections each.

3. Although the number of white and black patients in the service was approximately identical, many more Cæsarean sections were done upon the latter—114 to 69, while 30 to 11 required repeated sections.

4. The following types of operation were done:

121 typical conservative sections.
4 extraperitoneal sections.
1 postmortem section.
57 Porro sections.

5. The gross mortality was 5.46 per cent, but, upon deducting the cases in which death was not attributable to the operation, the net mortality was 3.45 per cent; or 4.07 per cent in the conservative and 1.82 per cent in the Porro sections.

All deaths, except one from hæmorrhage were due to infection.

6. The mortality was 13 times greater in the first 50 than in the last 133 cases—10 to 0.77 per cent. This remarkable diminution was not due to changes in operative technique, but to the avoidance of ascending infection by operating before the onset of or during the first hours of labor.

7. The conservative section late in labor is always dangerous, even if vaginal examinations have not been made; while the Porro section is relatively safe. The most important means of lowering the mortality of conservative Cæsarean section due to disproportion is by learning to determine before the onset of labor whether operation will be required or not.

8. The Porro operation is relatively safe even in infected or exhausted patients, as the absence of the involuting uterus hinders the spread of infection.

9. Disproportion due to contracted pelvis was the indication for interference in nine-tenths of the black, and in six-tenths of the white patients.

10. The several varieties of rachitic pelvis afforded the predominant indication in the blacks, as compared with the simple flat pelvis in the whites.

11. The most frequent non-pelvic indications were eclampsia and serious cardiac decompensation.

12. Cæsarean section is not the ideal treatment for eclampsia, and is indicated only in the rare instances in which the cervix is rigid and undilated and venesection has not led to improvement.

13. It is likewise only rarely indicated in placenta prævia. We have done but one section in 66 cases, and regard the rubber balloon as the best treatment.

14. Generally speaking the patient should be sterilized at the third section, either by amputating the uterus or by an operation upon the tubes.

15. We make the abdominal incision below the umbilicus, as it permits amputation of the uterus or operations upon the appendages, when necessary, without extending the incision.

16. The uterus should be incised *in situ*, and eviscerated before incision only in the presence of infection. Our experience indicates that in normal cases the latter procedure increases the incidence of infection.

17. The uterine incision should be sutured in layers, and the greatest care taken to insure the closest approximation of the peritoneal margins.

18. The uterine cicatrix ruptured once in 48 women with repeated sections, as well as in 12 deliveries through the natural passages subsequent to section. The frequency of its occurrence is probably exaggerated, so that the dictum "once a Cæsarean always a Cæsarean" is not necessarily correct.

On the other hand, the possibility of rupture must always be faced and constitutes the strongest argument against the unnecessary employment of Cæsarean section for non-pelvic indications.

19. The placenta was inserted upon the anterior wall of the uterus in two out of every five of our cases. Consequently, it is frequently involved in the uterine incision. This has no other significance than a momentary gush of blood.

20. The delivery of an asphyxiated child occurs less frequently than is generally believed. Somewhat over one-half of our children cried immediately after delivery, and only 7 per cent were deeply asphyxiated.

21. Notwithstanding the extraordinary value of pituitary extract in stimulating uterine contraction, pronounced atony with danger of death from hæmorrhage is still to be reckoned with, and necessitated amputation of the uterus in two of our patients.

22. Uterine adhesions were absent in one-quarter of our repeated sections, and were extensive in one-third of them. They are not necessarily the result of infection, as the puerperium was normal in 36 per cent of the cases in which they developed. In many instances they appear to be associated with imperfect approximation of the uterine wound or with other traumatic factors.

23. The old superstition that boys originate from the right and girls from the left ovary can be definitely discarded. In two-thirds of our patients the corpus luteum persisted until the end of pregnancy, and its location bore no relation to the sex of the child.

24. Finally it should be remembered that Cæsarean section is not devoid of danger, and is relatively safe only when done under appropriate conditions before the onset or during the first hours of labor.

As the uterine cicatrix constitutes a *locus minoris resistentiæ* in subsequent pregnancies Cæsarean section for other than pelvic indications should be performed only when absolutely necessary.

It is my conviction that the operation is being abused throughout the country, and if accurate statistics as to its results were available that it would be found to be accountable for many unnecessary maternal deaths.

It should be recognized that, although it is frequently the easiest manner of delivering the patient in the presence of various abnormalities, it is not always the safest, and that ideal results are obtained in only a few clinics.

MODERN METHODS IN HANDLING HOSPITAL STATISTICS[1]

By Raymond Pearl,
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I. Introduction

To an ever-increasing degree modern science is becoming quantitative in its methods of thought and activity. The history of science from the beginning shows that the earliest development of any discipline is purely qualitative and that only as it emerges from this state and passes over into the quantitative phase, in greater or less degree, does it begin to take an assured place in the hierarchy of the established sciences. Recent examples of this change from a qualitative point of view are found in psychology and sociology. With the development of knowledge and of an appropriate technique eventually any natural phenomenon which can be observed can also be quantitatively measured. The entire history of medicine shows that there has been almost from the first an earnest desire and effort, on the part of some of its leaders, to develop quantitative modes of thought and methods of work. The large measure of progress which has been made in this direction is sufficiently evidenced by the number of items of diagnostic and clinical significance which are measured and recorded in quantitative terms.

The analytical treatment of the quantitative data of medicine has developed far more slowly than the appreciation and collecting of the data themselves. This fact is neither surprising nor peculiar to medicine. Only in the last decade of the nineteenth century with the pioneer work of Galton, Weldon and Pearson, did there begin the application of really adequate statistical methods to any sort of biological problem. Since that time the development has been very rapid in many of the fields of general biology. In medicine there have been differences of opinion, as would be expected, between leaders, as to the significance and importance of a really scientific statistical calculus in the field of medicine. The reactionary and the progressive viewpoints in this regard cannot be better set forth than in the following quotations from two clinicians of the foremost rank. In 1912 Sir Almroth Wright, in discussing the statistical method, said:[2]

> These general considerations have prepared the way for bringing forward the suggestion that the ordeal of minutely accurate quantitative statement which is always floating before the vision of the statistician should in the field of clinical medicine be frankly abandoned. This would mean recognizing that it is, in medicine, impossible by the method of cumulative experiments either (a) to detect minute differences, or (b) to arrive in any case at an accurate quantitative conclusion. . . . . Where there is a conflict of opinions between observers the proper course to pursue is to appraise the relative weight of the authorities who are ranged over against each other.[3]

[1] Papers from the Statistical Department of The Johns Hopkins Hospital, No. 1.

[2] Wright, A., and others. Observations on the pharmaco-therapy of pneumococcus infection. Lancet, 1912, (2), pp. 1701 and 1704.

[3] It should be pointed out that Sir Almroth Wright's strictures upon the statistical method have been dealt with by Greenwood (Lancet, 1913, Jan. 18) in a wholly adequate, and, for such persons as are capable of logical thought, final manner.

In 1920, Lawrason Brown said:[4]

None of you will contradict me when I say that statistics are very dry, but some of you may dispute me when I say that only by statistics does the world, lay or medical, advance. Consider what knowledge is and you will see how inseparable it is from statistics. Medicine is no exact science, and diagnosis rests largely upon the law of probability which in turn is statistical. All scientific experiments are statistical arguments in favor of or in opposition to certain inductions or deductions. Further, statistics lend the authority that is necessary for their acceptance.

The trouble in medicine does not lie with the statistical method but with the medical men who do not know how to use it. I regret to state that I belong to this class and have felt keenly that in medical school I did not have an opportunity to attend a course on medical statistics. The day will come, gentlemen, when such courses will be given, when the law of probability will help in diagnosis, when the coefficient or correlation, now explained by most authorities in such terms that in a few minutes my idea of my relation to my surroundings has become totally insufficient—when, I say, all these things will be understood by the medical graduate. At that time medical men will cease to do such foolish things with statistics as to try to add cabbages and cows, or, what is nearly as bad, to try to solve problems in heredity by finding how many parents had the disease from which the offspring suffers without due respect to many other very important and possibly contradictory details. What would you think of a bookkeeper who after years of personal experience would gather up the bills in the cash drawer and go to the bank with the statement that his personal experience led him to believe that the roll of bills amounts to $1000. The receiving teller would quickly apply the statistical method and few would venture to side with the bookkeeper, no matter how large his experience had been.

Do not misunderstand me. This is not an argument in favor of dry statistical articles which we all prefer to avoid reading. But if I can make you see how important it is for us to cease using the pet phrase "my personal experience" except when we have sufficient data to support it, I shall have accomplished what I had hoped for.

General experience with other branches of science would make it seem reasonable that the following propositions are true, and should be emphasized in the teaching of medical students:

1. That there is no inherent reason why medicine in every one of its phases should not ultimately become in respect of its methods an *exact* science, in the same sense that physics, chemistry, or astronomy are to-day exact sciences.

2. That this goal will be reached in exact ratio to the extent to which quantitative methods of thought and action are made an integral part of work of every sort of medicine.

3. That no number or figure can be said to have any final scientific validity or meaning until we know its probable error, the "probable error" being the measure of the extent to which the number will vary in its value as the result of chance alone.

For at least three centuries it has been the custom of hospital authorities to prepare and publish routine statistics regarding the activities of their institutions. These statistics usually comprise only the following general sorts of items: Number of admissions, nature of ailment, number of treatments, number discharged either dead or alive, improved or unimproved, and other similar material.

It is interesting to speculate as to why such statistics are published. I believe the clue is found in the history of the matter. Hospitals began as public or private charities, to the support of which financial contributions were solicited. The evolution of human nature having proceeded no farther than it had, it was felt necessary to furnish at frequent intervals documentary evidence of the moral rectitude of those persons responsible for the disbursement of the donated funds. The best possible evidence that someone has not absconded, or misused the institution's resources is statistical proof that the hospital has been performing its proper function of admitting, treating, and discharging patients. Beyond this essentially moral purpose it is difficult to discover that the type of purely routine hospital statistics now referred to has, will, or can serve any useful purpose. I am aware that at various times statisticians have presented memoirs and reports upon hospital statistics of this sort, but in general such reports appear to me essentially to have done only one or the other of two things: Either (1) they have shown that the treatment of disease in hospitals is more effective now than it was at some earlier period; or (2) they have attempted to deduce conclusions as to the incidence in the population of different forms of disease. Regarding the first of these points it may fairly be said to fall under the sort of activity which William James called "the painstaking delineation of the obvious," a practice which has deservedly brought statistical science into disrepute upon more than one occasion. On the second point it need only be said that to attempt any deductions from hospital records as to the normal incidence in the population of either morbidity or mortality is an obviously fallacious procedure, since the hospital population is a highly adversely selected sample of the general population. This fact has, of course, been appreciated widely. There have been a few scientifically sound and valuable contributions to knowledge based upon purely routine hospital statistics, but the number is meager.

It is obvious, in the nature of the case, that a large general hospital comes by way of a literally enormous number of facts about disease and its treatment, many of which facts are either now expressed in numerical form, or could be easily so expressed. In a broad sense, disease is a biological problem, to the solution of which every case can be made to contribute some mite of data or knowledge. The case history is the tangible form which the record of these individual facts takes. When, however, a hospital has been running any significant length of time, the number of these individual case histories becomes so vast that nothing can be done with the wealth of data which they contain except by the application of the statistical method. Now the modern statistical calculus is a highly intricate and complex branch of higher mathematics. It is unreasonable to suppose that the same person is likely to be, except in the rarest instances—of which a brilliant example is Dr. Major Greenwood of the British Ministry of Health—an expert in both medicine and statistical mathematics. Yet the investigator in medicine, by force of the very

[4] Brown, Lawrason. American Review of Tuberculosis, September, 1920. Volume IV.

nature of his data, is compelled to use the statistical method in analyzing and presenting his results. The result is sometimes a little sad if judged by the same canons of scientific method as those by which the published work of a physicist, for example, is judged. But if we leave aside these deplorable cases, happily few in number, of wrong conclusions from data, and consider only those results which may be regarded as correct so far as they go, the trained statistician is able to see in a great many cases how, by proper mathematical treatment of the existing data, it would have been possible to get a much deeper insight into, and much more useful knowledge about, the problem than the statistically untrained medical man was able to get.

The case is plainly one calling for the cooperative endeavors of specialists in distinct fields. Since a modern hospital moves and has its being in the idea and practice of cooperation between various medical and surgical specialists it would seem a singularly happy environment in which to develop cooperation, having as its ultimate object the best use for the advancement of the science of medicine of the quantitative data which its records furnish. This means that the statistical records of a modern hospital should be supervised by and their investigational analysis undertaken in cooperation with an expert statistician.

II. Some General Principles to Be Observed in Developing Statistical Work in a Hospital

1. Since one cannot get out of any machinery of statistical treatment anything intrinsically different from what went in, it follows that accuracy and completeness of the initial routine statistical data collected in a hospital are matters of prime importance, in which everyone interested in the work of the hospital is also *per se* interested, and needs only to be shown where any improvement can be practically made, in order to give his cooperation to the attainment of that improvement.

2. In any old and well-established hospital the existing system of case record keeping is sure to be so intricate and has so many ramifications, that changes made in it, if any, should be very gradual, and only with the complete and hearty approval of everyone involved. At the same time, however, it should be recognized that there have developed in recent years great advances in the art or science (as one pleases) of efficient record keeping. Some of the older hospitals in this country operate with a general record system which unquestionably violates nearly every one of the best established canons of modern office practice, and which would not be tolerated for a moment by any equally large, properly organized and managed, business concern.

3. The statistical method is a *technique*, a means of getting light on complex problems and not an end in itself, and therefore it is essential that before it be applied there be a clear definition of the problem to be attacked, whether biological, medical, pathological, surgical, or other. Unless there is a real problem, with real meaning, to be solved, the application of the statistical method is as futile and sterile as would be the application of any other technique.

4. The development of research work along statistical lines in a hospital should be just as rapid, and only as rapid, as the results obtained demonstrate the value to the advancement of medical science in general of this type of work.

5. Since the statistical technique is a highly complex one, requiring expert knowledge for its correct and most useful application, an expert statistician should certainly be a member of the staff of any hospital attempting to do any research work, and should be called into consultation in regard to the methods and form of research communications based upon the statistical data of the hospital, in order that duplication of effort, and the commission of egregious errors in drawing conclusions from quantitative data may be avoided. Furthermore, for the benefit of medical science in general, and in the interest of better administrative and professional operation of the hospital itself, every large hospital should have at least one properly trained person to attend to the assembling and tabulation by adequate modern methods the routine statistics of the hospital.

III. Functions of a Statistical Department in a Hospital

The statistical department, in accordance with the above outlined general principles, should perform the following functions, either directly or in a supervising and directing capacity:

1. *Assembling and Tabulating Routine Statistical Data.*—The case history room is the brain of a hospital. There are finally assembled all the records that exist of the medical (using the term in the broadest sense) activities of the institution. To make histories available for future reference for whatever purpose, the data which they contain must be classified and indexed in some manner or other. Further, if any comprehensive view is to be had of the medical activities of the hospital, these data must from time to time be tabulated in a great variety of ways to meet the variety of needs and interests certain to be reflected in the intellectual activities of the staff of any large teaching hospital. Now, as presently will be shown in detail, this indexing and tabulating can all best be done by modern "mechanical tabulation." If it is so done, an incalculable, but certainly very great, addition will be made to the efficiency of the hospital's work. There is no more depressing sight to the statistician, familiar with efficient methods of handling large masses of data, than to see a poor interne struggling with the index and bound volumes of case histories, painfully and slowly assembling on great sheets of paper all the records the hospital has about some particular diseased condition. Months of labor may be, and all too often are, spent in the mere *assembling* of a small collection of data from the case histories, which a properly organized statistical department, with facilities for mechanically indexing, sorting and assembling the data, could easily furnish in a half day. So, then, the first duty of a hospital statistical department should be the transferring to punched cards for purposes of indexing, assembling, and tabulating, of the basic routine facts from all case histories.

2. *Organization of Special Departmental Records.*—The routine statistical records discussed in the preceding section form only the skeleton of the whole statistical structure which one can see developing in hospitals. Different departments and services will want, as a routine matter, much more elaborate analysis and indexing of the facts of their own cases than would be either proper or possible as a basic uniform procedure for the hospital in general. An important function of the statistical department will be to aid in the development, proper handling, and mechanical tabulation of these special and detailed but still routine statistics. An illustration will be given further on in the paper of the possibilities of this type of statistical development, in connection with the prostatectomy histories of the Brady Urological Institute of this hospital.

3. *Consultant Service.*—A very large percentage, indeed nearly all, published papers based upon hospital or other medical records, contain a greater or smaller amount of statistical data. In many cases these papers are written by men who know practically nothing about the proper treatment of statistical data in such a way, on the one hand, as to lead to correct conclusions, properly fortified with probable error measures of reliability, or on the other hand, to get the maximum of useful information out of the data themselves. As has already been pointed out this difficulty is inherent in the nature of the case, medical training being as it now is and as it is likely to be for some time to come. It implies no criticism of anyone, but is merely one expression of the patent fact of the specialization which exists in all fields of modern science. The best solution of the difficulty would appear to be to build up such a spirit of cooperation between the statistical and other services of a hospital, that the former would regularly be called upon, in a consulting capacity, to aid in the analysis of the purely statistical phases of the research work done in the institution. This would involve a wide variety of service, ranging all the way from simple advice as to the best form in which to present statistical tables or charts, to long computations to bring out in the best way the significance of the results. In this field the highest intellectual equipment and expert knowledge of the statistician will be called for. But there can be no doubt that in any hospital where such a plan of cooperation is effectively utilized, the quality of the research output will be immeasurably raised. It must, of course, be understood that in this field, as in most others, cooperation is a delicate flower, whose growth cannot safely be forced. One proceeds most rapidly by going slowly. Our experience in The Johns Hopkins Hospital indicates, however, that as soon as the underlying viewpoint and significance of this sort of consulting service is well understood by the staff, the requests for it come along quite as rapidly as a small statistical staff finds desirable.

4. *Research.*—The properly organized hospital statistical department will have as its head an investigator, who will see in the wealth of material which exists in the records possibilities, undreamed of by the non-statistical clinician, of throwing light on obscure problems of medicine and surgery. The carrying on of special biometric investigations, based upon hospital records, is one of the highest functions which a statistical department can perform.

IV. The Commonest Defects in Hospital Records

The fundamental and basic element in a hospital's records is the individual case history. Upon it depends any and all useful information, whether statistical or otherwise in character, which may be wanted for any purpose whatever. It is, therefore, of the highest importance that hospital histories conform to the best standards of scientific record making, on the one hand, and of modern office practice on the other hand. There are relatively few hospitals where the highest standards in either of these respects are even approximated.

From the standpoint of scientific routine record taking, case histories are most glaringly defective in what they *fail* to record about the patient. It is by no means impossible to find case histories that fail to record the sex of the patient, while any indication of what *kind* of person the patient was, in the common sense of the word, whether fat or lean, white or colored, rich or poor, young or old, etc., is all too frequently kept a deep secret from any subsequent reader of the history. Again, even in the special medical portions of the history the writer forgets, with almost unbelievable frequency, to make any record of highly important facts.

The root of such difficulty apparently lies in the method by which case histories are written. The general scheme or outline which a history is to follow resides, far too often, in the head of the history writer, and there only. And heads, especially of human beings, do vary so! The remedy is patent. Any hospital or service that desires to put its clinical records on the case record form for gall-stone cases, for example, there have printed a series of *standard* history forms, which will cover not merely general routine facts common to all diseased conditions, but special forms as well, for at least all of the more frequently occurring conditions. These blank forms will contain definitely indicated spaces in which some statement of fact *absolutely must be recorded in every single case.* If on the most scientific basis will as a first step draw up and is printed the question, "Did this patient ever have typhoid?" or the equivalent of this question, and if furthermore every worker in the service clearly understands that any history for which he is responsible that comes into the history department, with any blank spaces in its standardized portion, will not be accepted for filing, but will be forthwith returned to him for completion, future students will not be under necessity of having a "No information" column in their statistical tabulations relative to this point.

One realizes perfectly that any suggestion in the direction of standardizing case history writing, by the process of putting into operation methods which have been found sound and useful in other branches of science and in modern business, will at once be scornfully or even derisively received by some. It will be argued that any such process tends to cramp their individuality. This argument is perfectly valid. It will inordinately cramp such portion of their individuality as finds

its expression in carelessness, inaccuracy, forgetfulness, and inattentive observation. In so far as it is desirable to foster and preserve these intellectual qualities, and embalm their results in the permanent archives of a hospital, clinicians and surgeons should be encouraged to go on writing histories in the old way.

Furthermore, the argument will be made that the writer, a layman, has no competency or right to discuss at all the manner in which case histories are written, because being a layman he can possibly know nothing about the highly esoteric art of medicine. But here a little clear thinking is needed. The science and art of making accurate, comprehensive, and essentially complete records of natural phenomena is not exclusively nor even particularly a branch of the science or art of medicine. It is much broader and more basic and is, in every one of its logical and epistemological principles, common to all sciences. To these principles of scientific record making many persons, including the writer, have devoted many years of study and thought. And it is just precisely *that* field, not medicine, that we are talking about when we are discussing the method of writing case histories.

It is, of course, to be understood that no blank form, however carefully it may be devised, can ever suffice for the recording of the *whole* history. There must be some portions written or dictated with entire freedom from Procrustean rigidities. The reason why this is so is plain. One of the chief characteristics of living things, whether men or mice, is that they vary individually. But formal blanks do not vary. An invariable phenomenon cannot fit a variable one. But this is no valid argument against having certain essential parts of the history recorded in standardized form. There are certain facts that everyone will agree ought to form a part of every history case which is to be permanently preserved. It is that class of facts which should be recorded upon standardized formalized sheet or sheets incorporated into each history. Then *in addition* the clinician may write or dictate as much more as he likes, in an entirely free untrammeled style. The formalized portion merely serves as the schema of the whole, to make sure that no point of importance for future students is left out, because forgotten, in the greater interest of other more immediately exciting features of the case.

Turning to the question of the way case histories are handled after they are written, which is essentially a matter solely of business or office management and not of medicine, there are two glaring defects in the common practice. These relate, first, to the fixation of responsibility for the recording of each item in the history, and, second, to the filing of the completed histories. From every point of view, whether of administration, research or other, it is of the highest importance that future students of a hospital's records should know who is responsible for statements appearing in a history. How often has one seen and heard long and inconclusive debates as to what interpretation was to be put upon some statement in a history as to a clinical finding? The decision all depended upon who originally was responsible for the statement. If it were the considered verdict of the wise and experienced old professor it was one thing; if it were the snap judgment of the latest interne it was quite another. All this difficulty can be removed by inaugurating and practicing the principle that every sheet of a history shall bear upon its face the names of the person or persons responsible for what appears upon that page. Perhaps a word of caution needs to be added lest there should be some misunderstanding. Fixation of responsibility is not to be construed as an excuse for any weakening of the rigid canons of extreme objectivity in history or protocol writing, now generally taught in all first-class medical schools.

The purpose of *filing* case histories is two-fold: first, to preserve them, and, second, to do it in such a way as to make them most readily accessible to anyone who may in the future want to consult them. There can be no question that this latter purpose will best be served by the so-called "unit system" of case histories, in which the hospital's complete record about any one individual forms one separate and distinct volume. The advantages of this method of preserving histories over the far more common system of binding them up in great volumes in numerical or temporal sequence, are so obvious as not to need detailed exposition. Such a method of handling the completed records is really essential to their most efficient utilization, whether for statistical, investigational or any other purposes.

V. The Organization of the Routine Statistical Records of a Hospital

There are certain items of information which ought to be and generally are intended to be included in every case history. Some of these routine items are:

1. Case number.
2. Service number.
3. The patient's name.
4. Diagnosis.
5. Sex.
6. Social status (single, married, widowed, divorced).
7. Age.
8. Occupation.
9. Body weight.
10. Stature.
11. Race.
12. Birthplace.
13. Service under which patient was treated.
14. Date of admission to hospital.
15. Duration of stay in hospital.
16. Time from onset of diagnosed condition to admission to hospital.
17. Condition at admission.
18. General health of patient prior to present illness.
19. Whether there is any family history of the diagnosed disease.
20. Whether a first entry or a readmission.
21. Whether a free, a paying, or a part-paying case.
22. Condition at discharge.
23. Whether or not an autopsy was performed.
24. Autopsy number, if any.
25. Nature of treatment.
26. Complicating pathological conditions, additional to the one diagnosed.

In an ideal system of handling hospital records each history should be cross-indexed under each one of the following items

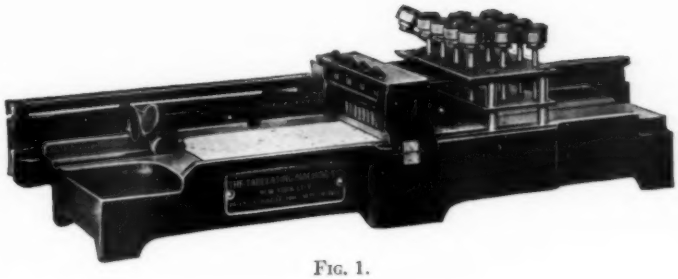

FIG. 1.

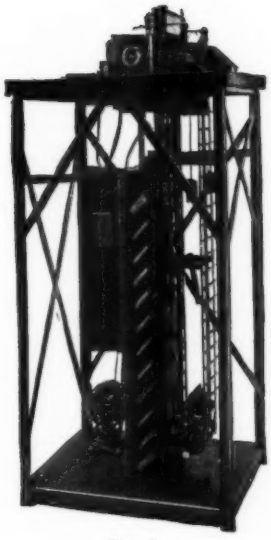

FIG. 2.

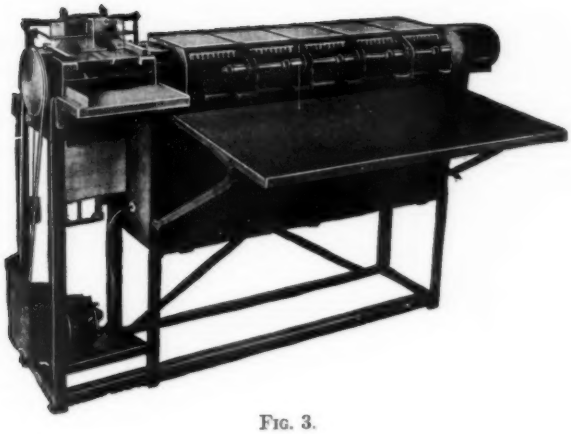

FIG. 3.

in the above list at least: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 21, 22, 23, 24, 25. Of course, nothing like such complete cross-indexing as this is even attempted, not to say accomplished.

There is only one method now known, whereby in a practical way such an amount of cross-indexing can possibly be accomplished. That method is to handle the routine information by the modern system of mechanical tabulating and indexing. On this system the original records are transferred, by means of a machine called a "key punch" (*Cf.* Fig. 1)[8] to cards, the record on the card appearing as a series of punched holes. Then, by means of another machine, known as a "sorter" (*Cf.* Fig. 2), the punched cards can be mechanically sorted, at a rate of 250 cards per minute, into any desired arrangement relative to any character or item of information recorded upon the cards. Let us suppose, for example, that someone wishes to assemble for study all the cases of lobar pneumonia which have been treated in the hospital. Suppose the diagnostic code number for lobar pneumonia is 102. One has then only to run the cards through the sorter relative to the field designated "diagnosis" and pick out, after the cards have been mechanically arranged in numerical order, all those bearing the punched number 102 in the diagnosis field. These 102's will all be together in one bundle, and they will be all the lobar pneumonia cases in the hospital's records. Each card will bear the case number, from which, of course, the original histories can be consulted if one desires. If one particularly wishes to study the lobar pneumonia of negroes, he need only take his bundle of "diagnosis 102" cards, run through the sorter again relative to "race" and he will in a few moments have all the cases of this disease in negroes separated out by themselves. Suppose he is further only interested in lobar pneumonia in negro children under 5 years of age, say. He need only take his bundle of negro lobar pneumonia cases and put them through the sorter again, retaining this time only those falling into ages under 5. He gets his results at the rate of 250 a minute. Compare this with the laborious process that would be involved in assembling by hand from an ordinary card catalogue of hospital case records the case history numbers of *all* the cases of lobar pneumonia in negro children under 5 ever treated in the hospital. The comparison is as of hours with weeks or even months, if the histories be numerous.

Again, suppose that a complete group of like case histories has been assembled by painfully laborious hand processes, and one wishes then to make a statistical tabulation of the facts they contain. Weeks or months may easily be, and often are, spent upon the process. But if the records are upon punched cards, the pertinent cards, which have been mechanically assembled, need only be run again through another machine, known as a "tabulator" (*Cf.* Fig. 3) and the results relative to any desired category of information will be mechanically counted and tabulated, with great rapidity and absolute accuracy, and the columns of figures will at the same time be added.

Examples of the usefulness of this method of handling a hospital's statistics could be multipled indefinitely. But instead of further considering hypothetical cases, let us proceed specifically to the concrete problem of the organization of card forms for the routine statistics of a hospital.

Figures 4 and 5 show the necessary card forms.

A detailed explanation of these forms and the manner in which they will operate is necessary.

A. THE PRIMARY CARD

Taking first the primary card form it may be said that this will presumably be printed upon manila stock. Each group of numbered columns lying between vertical rules is technically known as a "field" of the card.

Across the top of the primary card is written, or typewritten, (a) the full name of the patient, (b) a letter or number designating the service—whether medical, surgical, obstetrical, etc.—in which the patient was admitted; and (c) the number of the case in that service, on the assumption that in addition to the general hospital serial number of each case there is also a special indentifying service number. If a particular service does not specially number its cases, this space will be left blank.

1. The first field is a six-column one and in it is punched the general serial number of the case history. This number identifies the history and the card, and enables one to pass directly from the card to the original history. If a case, for example, is number 12,347 in the hospital's series this field will be punched 012,347. A six-column field permits the separate serial numbering of 999,999 cases. When this number is passed, presumably the cards for the second million would be printed upon stock of another color.

2. The second field of five columns records the diagnosis of the patient's chief or primary ailment. This result is attained by the use of a code of diseases, each pathological condition it is desired to distinguish being given a separate number. A five-column field permits of 100,000 different discriminatory pathological statements. It is to be understood clearly that in this field on the primary card is recorded only what the case history states to be the primary or fundamental pathological condition which the patient presents. The question of the recording of associated and complicating conditions is dealt with below (p. 190). In preparing the nosological code the best advice of the clinicians, surgeons, etc., will, of course, in all cases be taken.[9] The field is made larger on

[8] The most generally useful and flexible system of mechanical tabulation now available is that known as the Hollerith system, from its inventor, Mr. Herman Hollerith. The machines of that system are the ones illustrated in this paper. Further information about these machines may be obtained from the manufacturers, The Tabulating Machine Co., 50 Broad St., New York City. It may be of interest to medical readers to know that a distinguished medical man, the late Dr. John S. Billings, had a great deal to do with the initiation and early development of this invention. He was a close friend and adviser of Mr. Hollerith all through the early stages.

[9] A disease code for use in mechanical tabulation has been very carefully worked out in the Surgeon-General's Office by Major Albert H. Love and his associates.

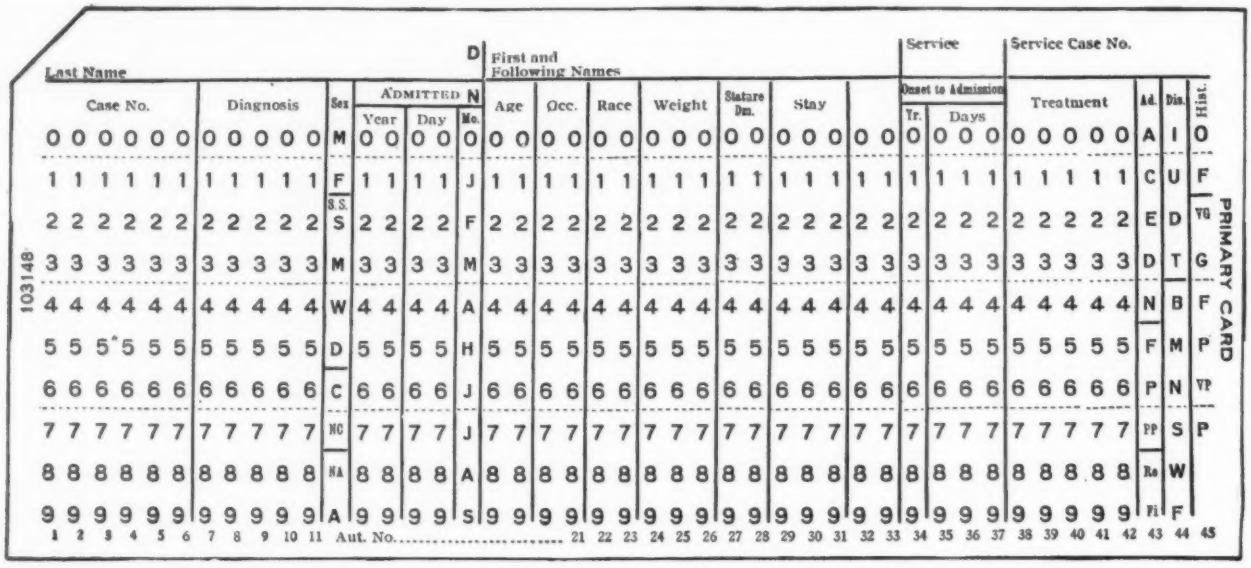

FIG. 4.—First or face card form for mechanical tabulation and indexing routine hospital statistics.

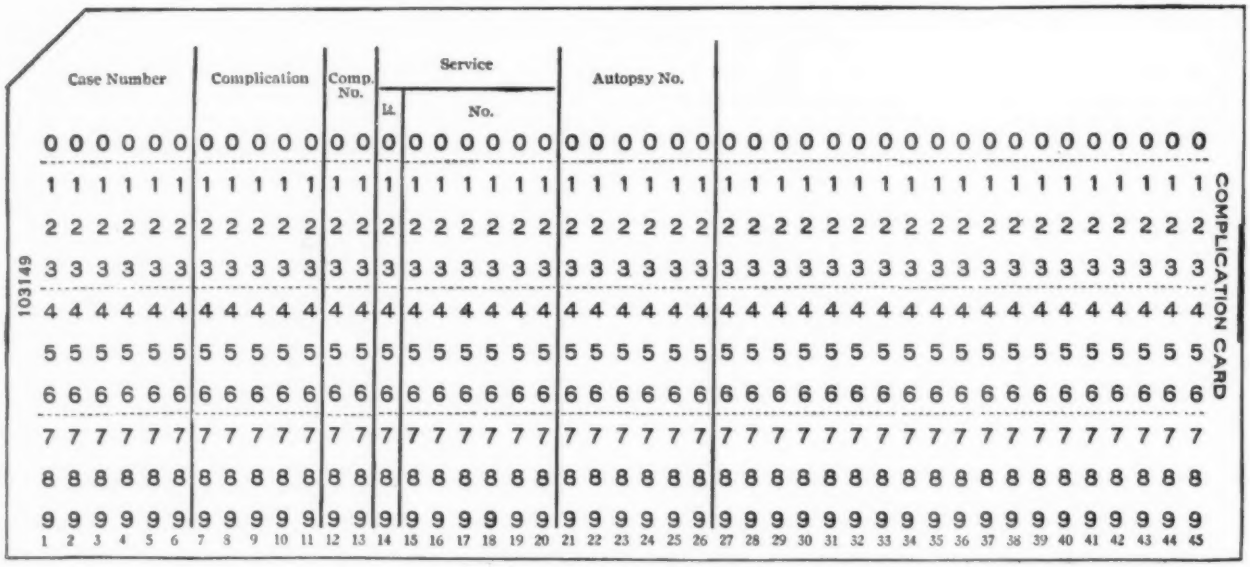

FIG. 5.—Second or supplemental card form for routine hospital statistics.

the card than there is any present need for, to allow for development of the subject and consequent changes in viewpoint.

3. The third field of one column is a "split field" so-called, and records the following information:

(a) Sex of the patient, male (M) or female (F).

(b) Social status, whether single (S), married (M), widowed (W), or divorced (D).

(c) Whether (C) or not (N.C) there were complicating pathological conditions in this case besides the primarily diagnosed condition given in the second field. The presence of this information makes it possible by a single run of the cards through the sorter to separate the uncomplicated cases of a particular disorder from the complicated ones.

(d) Whether (A) or not (N.A) there was an autopsy made in this case. At the bottom of the card is written under this field, in the event that an autopsy was made, its serial number.

4. In the fourth field of five columns is punched the year, month, and day of admission of this patient to the hospital.

5. In the fifth field is punched the patient's age in years.

6. In the sixth field is punched, according to a code, the patient's occupation.

7. In the seventh field is recorded the patient's race, according to the ethnological code used by the U. S. Bureau of Immi-

gration. This information as to race necessarily also covers color.

8. The eighth field of three columns records the weight of the patient on admission, in kilograms (or, of course, if one prefers, in pounds). The most progressive of modern hospitals record weight on admission as a routine procedure.

9. In the ninth field of two columns the stature is punched in decimeters (as close as will ever be used in statistical groupings) or inches, if one prefers as a routine to use common rather than metric measures. The stature in centimeters may be written at the top if the field of the more exact record is desired.

10. The tenth field of three columns records the duration of the patient's stay in the hospital in days.

11. In the eleventh field of three columns is punched the designating letter (by code) or number of the service to which the patient is admitted for treatment, whether medical, surgical, pediatric, etc. The purpose of this is to enable the ready assembling, for any desired purpose, of all the cases in a particular service.

12. In the twelfth, five-column field, is recorded the duration of time in years and days as stated in the history, between the first onset or appearance of the diagnosed condition and the admission of the patient to the hospital for treatment.

13. The thirteenth field of five columns is a very important one. It records, according to a code which can be made as elaborate and detailed as the clinicians and statistician in consultation determine to be desirable, the nature of the treatment given in the hospital to this particular case. Five columns permit of 99,999 separate discriminatory items to be recorded in this field. Suppose, for example, one wishes to study the pneumonia cases in which digitalis was administered, in comparison with those in which this therapeutic measure was not employed. To pick out by hand from all the pneumonia cases the material according to this arrangement would involve an amount of labor which would deter the most enthusiastic young interne. But, mechanically, through the medium of this field, it can be very easily and quickly accomplished.

14. The fourteenth is a split single column field. It records the following information: (a) The nature of the case upon admission, whether an acute illness (A), a chronic (C), an emergency or accident case (E), a case admitted for purposes of diagnosis (D), or a normal person (N), as for example a normal pregnant woman admitted to the obstetrical service for delivery. (b) The financial arrangements of the patient with the hospital, whether a free patient (F), paying (P), or partly paying (P.P).[1] (c) Whether this case represents the first admission of the patient to the hospital, or whether it is a readmission.

[1] In some hospitals, of course, this information under item 14b would not be pertinent and could be omitted or replaced by something else.

15. The fifteenth field is also a single column split, and records:

(a) The condition at discharge, whether improved (I), unimproved (U), dead (D), or transferred to some other service or hospital (T).

(b) The location of the patient's residence, whether in Baltimore (B), or in Maryland outside of Baltimore (M), or in the Atlantic seaboard states north of Maryland (Pennsylvania, Delaware, New Jersey, New York and the New England States) (N), or in the Atlantic seaboard states south of Maryland (District of Columbia, Virginia, the Carolinas, Georgia, Florida) (S), or in some other part of the United States not specified above (W), or in a foreign country.[2]

16. The sixteenth and last field on the card is again a single column split field. It records the following information:

(a) Whether or not (F and O) there is any statement in the written history as to family history of any particular disease in the patient's family. This information enables one interested in the influence of heredity on disease to pick out quickly the cases likely to be of any value to him.

(b) The general health of the patient prior to the present illness, as recorded in the written history. This information is punched according to the following or similar code:

Very good	never ill.
Good	minor ailments only.
Fair	average amount of sickness.
Poor	frequently ill.
Very poor	an invalid throughout life.

(c) Whether this card is a primary card. This is a technical point of interest only in connection with the filing of the punched cards.

This completes the description of the primary card. It records 31 different kinds or items of information.

B. THE SECONDARY CARD

The basic purpose of the secondary card shown in facsimile in Fig. 5 is to take care of the complicating diseases. An illustration from an actual case history will make the point clear.

A patient, X, was admitted to the hospital under the primary diagnosis of hyperthyroidism and adenoma of the thyroid. A double lobectomy was done. A post-operative broncho-pneumonia developed, and the patient died 14 days after the operation. At autopsy besides the broncho-pneumonia there were found clear evidences of (1) a cerebral embolus with softening, (2) chronic and acute verrucose mitral endocarditis, (3) multiple myomata of the uterus, (4) cystitis, and (5) fibrous pleurisy.

Now the primary card discussed in the preceding section of this paper would carry in the "Diagnosis" field only the

[2] The 15b field is obviously drawn up solely for The Johns Hopkins Hospital and would require modification for any other hospital. Some institutions may not desire statistical information as to place of residence, in which event this portion of the card may be used for recording something else.

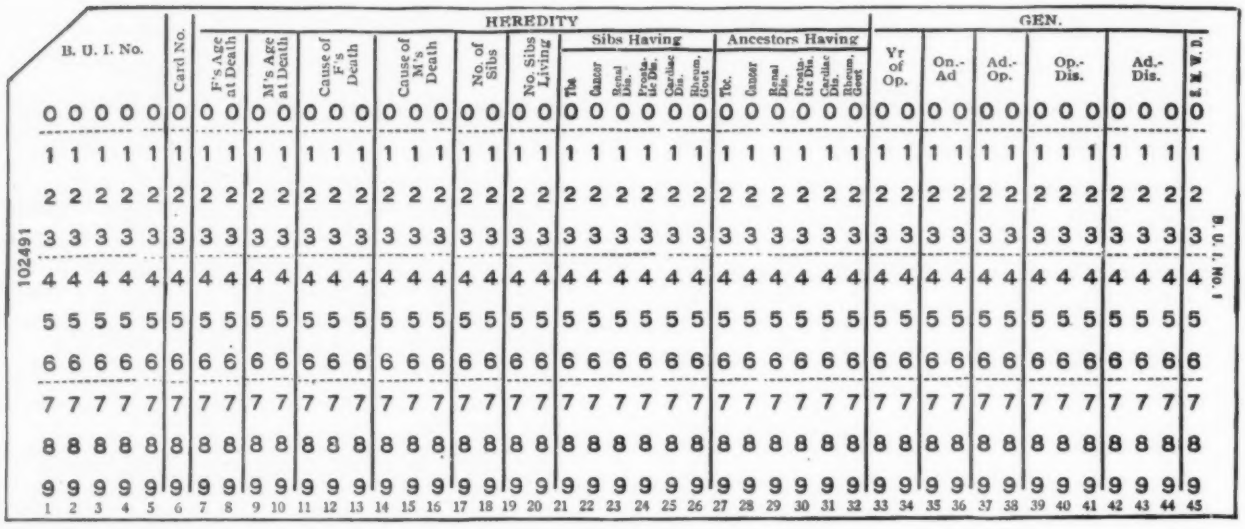

FIG. 6.

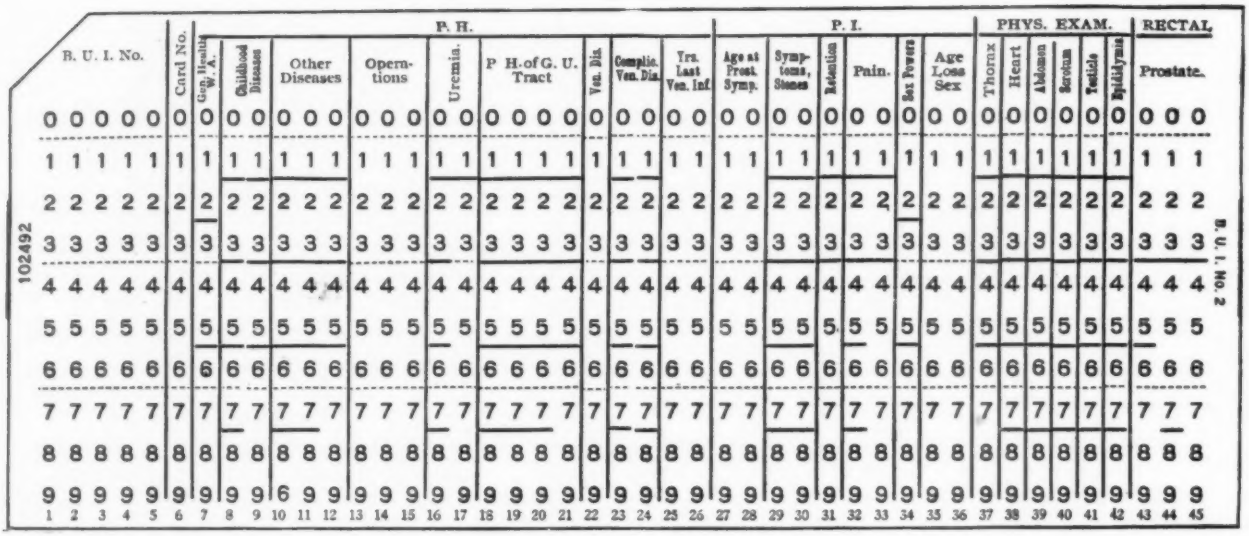

FIG. 7.

adenoma of the thyroid. Yet clearly for any adequate statistical records there must be included some account of the other complicating conditions disclosed by the history. This is done by punching as many of the secondary cards, shown in Fig. 5, as there are separate and distinct complications (that is, in the present case, one secondary card for broncho-pneumonia, one for cerebral embolus, one for endocarditis, one for myomata of the uterus, one for cystitis, and one for pleurisy). Each secondary card carries the same case number in the first field as the associated primary card, and will therefore automatically file with it. The "Complication" field on the secondary card registers with the "Diagnosis" field on the primary card. Therefore, when all the cards, both primary and secondary, are run through the sorting machine relative to this field, all identical diseased conditions, whether primary or complicating, will be brought together. Then by a second sorting of the cards the cases in which any particular disease, say broncho-pneumonia, was the occasion of admission to the hospital, can be separated from those cases in which this disease was a secondary complication.

The remaining fields on the secondary card are used to record additional information for which there was not space on the primary card. These include (1) the ordinal number of the complication as recorded in the history, (2) the service number which was written but not punched on the primary card, and (3) autopsy number, which also was written but not punched on the primary card.

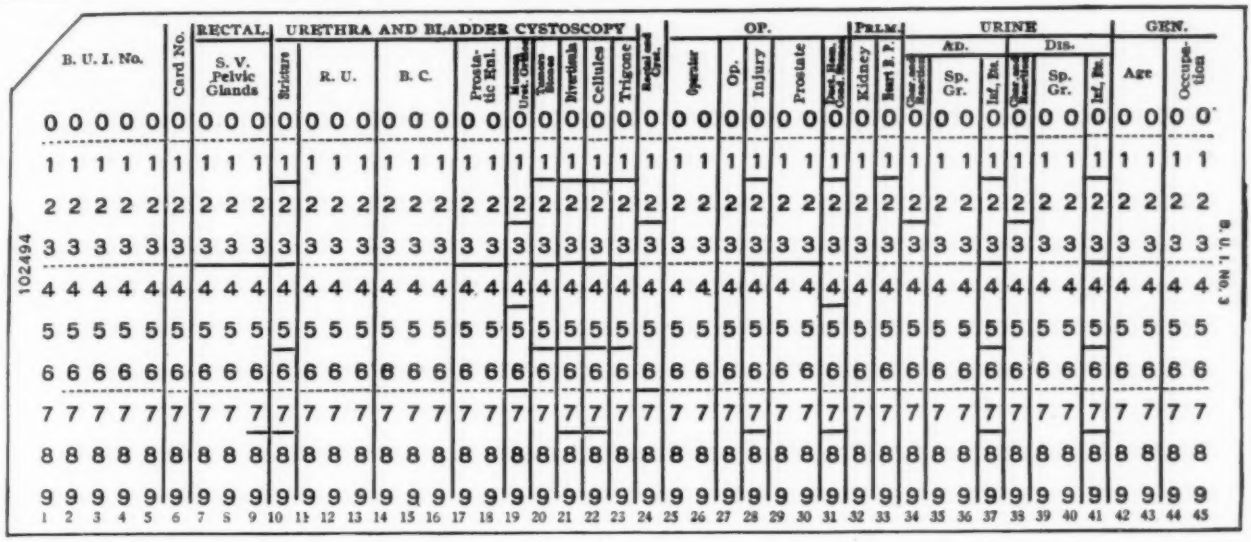

FIG. 8.

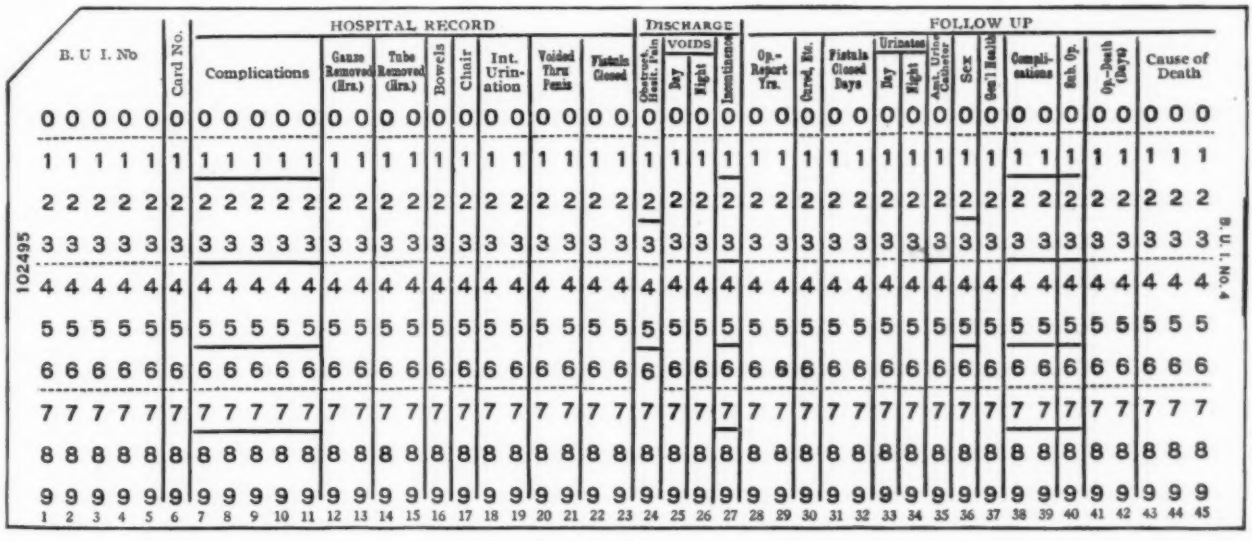

FIG. 9.

VI. AN EXAMPLE OF SPECIAL CARD FORMS

As was pointed out earlier the recording of information on punched cards may be very advantageously employed for detailed records, extending in scope far beyond what needs to be included in routine hospital statistics. Suppose for example that one wishes to make a thorough analysis and study of 1000 consecutive operations of the same sort. Card forms can be devised to carry all of the most detailed minutiæ of the case histories, and then, when the cards have been punched, the information can be tabulated in every conceivable manner for study and discussion, with a minimum of labor. It is to be expected that as a properly organized statistical department in a hospital becomes well established more and more work of this sort will be demanded of it.

As an example of this sort of thing Figs. 6 to 10 inclusive are introduced to show in facsimile a series of card forms which are now in use in connection with a monographic study of 1000 consecutive prostatectomies, which have been performed by Dr. H. H. Young in the Brady Urological Institute of The Johns Hopkins Hospital. Without a detailed description of the cards, for which this is neither the time nor the place, it is sufficiently evident from the card headings that a literally enormous amount of detailed information is included and made readily available for statistical study of these cards.

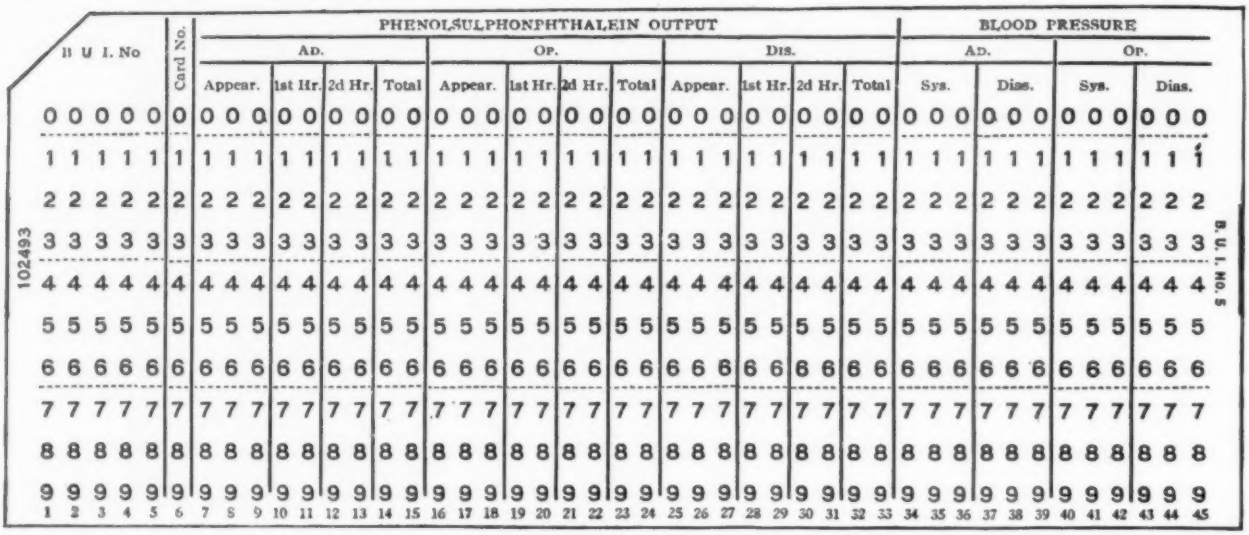

Fig. 10.

Figs. 6–10 incl.—Facsimiles of card forms for recording in detail case histories of prostatectomy in the Brady Urological Institute.

VII. The Organization of the Statistical Department of a Hospital

It seems desirable to set out in some detail the plans of organization, in respect of both personnel and equipment, of what might be regarded as an ideal or model statistical department in a modern hospital, where special emphasis is laid upon the research and teaching aspects of the work. It is to be understood that the plan is meant to represent an ideal, and need not and probably at best would not be inaugurated *in toto*, but would gradually develop to something like the end here sketched.

A. *Personnel.*—The statistical staff should include:

(a) A chief statistician, who would direct the work of the department. This individual should have had a thorough training in the mathematical theory of statistics, in modern statistical organization methods, and have a well-digested background of the biological and medical sciences.

(b) An assistant statistician, with similar training, but presumably not yet with such a background of experience as the chief.

(c) A computer.

(d) A card punch operator for routine work. As occasion demands, extra key punch operators may be taken on as temporary appointments for the completion of specific large undertakings.

(e) A sorting and tabulating machine operator.

(f) A draftsman.

B. *Location and Space Requirements.*—The statistical department should be physically contiguous to the case history department of the hospital. The following space would appear to be a minimum requirement for proper functioning.

(a) Two offices, one for the chief and one for the assistant statistician.

(b) A large room for (1) the card files, (2) the sorting and tabulating machines, (3) the key punch operator.

(c) A large room for the computing and drafting room.

C. *Material Equipment.*—There would be required at least the following:

1. One card sorter. Considering the large use of routine cards for index purposes, two sorters would be a great advantage to avoid delay at times of peak load requirements. The routine key punch operator would operate the extra machine.
2. One tabulator (5 bank machine).
3. Three key punches.
4. Two listing adding machines.
5. Four calculating machines.
6. Miscellaneous calculating and drafting equipment.

An organization of the sort outlined could care for the routine statistical work of a large hospital, and at the same time make large contributions on the research side.

VIII. Conclusion

In this paper I have endeavored to show:

1. That modern statistical methods have a definite and distinct place in the functional economy of a hospital, and particularly of a hospital where research and teaching form a part of the activities of the institution.

2. That the inauguration of appropriate methods of handling hospital records will enormously facilitate and economize all the work of the hospital which directly or indirectly comes in contact with or depends upon case histories.

3. That to accomplish these ends only a relatively small addition to either personnel or material equipment is necessary.

AN ATYPICAL BACILLUS PARATYPHOSUS B INFECTION

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INTRODUCTION

The purpose of this paper is to report the occurrence of what would seem to be an unusual infection in this country, and briefly to review the problems which arose in the attempt to classify bacteriologically the infecting agent. A clinical summary of the case will be given first, and this will be followed by a short discussion of the development of our knowledge of the group of organisms to which the causative agent belongs. An attempt will be made to classify it on the basis of our present knowledge of this group. The case to be reported is one of an atypical B. paratyphosus B infection.

CLINICAL HISTORY OF CASE

C. G., a colored male laborer, 45 years old, entered The Johns Hopkins Hospital, November 2, 1920, on the urological service, complaining of inability to void.

Family History.—Unessential.

Past History.—The patient remembers no illnesses except a rather severe attack of diarrhœa "several" years ago, which confined him to his bed for about a week. The stools were loose and contained mucus but no blood. He considers that his recovery was complete, although there has been a tendency to loose movements since, for which he thinks that sweets are responsible. He has never had typhoid fever, and on close questioning denies ever having had symptoms, other than the diarrhœa, which might be attributed to such an infection. He has received no typhoid vaccine.

He had gonorrhœa seven years ago. He has had nycturia (two or three times) for the past six or seven years, and this has gradually become worse during the development of the present illness.

Present Illness.—In 1913, following the attack of gonorrhœa mentioned in the past history, the patient developed a urethral stricture which became complete. It was necessary to use a catheter for some time. His condition gradually improved. Recently he noted that he was passing a continually smaller stream. Dysuria and hesitancy developed. Finally, during the month previous to admission, he became unable to void except with great effort, and then only a few drops at a time. Incontinence of urine resulted.

Physical Examination.—The patient was seen first in the genito-urinary dispensary where, after unsuccessful efforts had been made to pass the obstruction with catheters, he was advised to enter the hospital for operation.

On admission the general physical examination is reported as being essentially negative with the exception of a temperature of 99.5° F. which almost immediately became normal. An external urethrotomy was performed by Dr. William Jack and he was sent back to the ward from the operating room in good condition.

On November 3, the day following the operation, the temperature suddenly rose to 104° F. and there was marked tachypnœa. There was moderate abdominal distention. The spleen was not palpable. Blood examination: R. B. C. 3,784,000; W. B. C. 13,080; Hb. 70%. Differential W. B. C. Count: Pm. N., 65%; Pm. E., 1%; Small Mononuclears, 20%; large Mononuclears, 9%; Transitionals, 1%.

Urinary examinations.—S. G. 1.010. There was a heavy trace of albumin and numerous leucocytes. No casts or red blood cells. Guaiac reaction negative. Phthalein output 55% in two hours. *Blood urea:* 24 mgm. per 100 c. c. plasma. *Blood CO_2:* 40 Volumes per cent. *Blood cultures:* B. paratyphosus B (atypical); about 3 colonies per c. c. of blood. *Urine cultures:* B. paratyphosus B (atypical). *Stool cultures*—repeated on numerous occasions—negative for typhoid and paratyphoid organisms.

Course in Hospital.—The clinical picture presented by the patient was confusing to those seeing him daily. At times he was in a typical typhoidal state, at other times the picture was rather that of true sepsis. The leucocyte count ranged from 7880 to 17,000. The polymorphonuclear percentage varied from 69 to 83. The large mononuclear and transitional elements were fairly constantly around 10%; the small mononuclear were from 7% to 20%. The specific gravity of the urine varied between 1.008 and 1.015. Albumin was present (+). Many pus cells. Some mucus. No casts or red blood cells. The stools varied in number from 1 to 15 a day, soft—not especially characteristic microscopically. The guaiac test for blood was negative. The temperature for the first 11 days in the hospital was almost continuously high, usually ranging from 102°-104.5° F. On three occasions during that time it was as low as 99.5° F. After November 13 (eleventh day in the hospital) the curves became septic in type, the temperature almost reaching normal in the mornings and rising to 103° or 104° in the evenings. No bradycardia.

The following note is found in the history, dated December 2d (28th day of the disease): "Classical typhoidal state; dull; mental reactions very slow. Sordes on lips and teeth. Pulse soft. Respiration a little rapid and deep. Abdomen distended. Intestinal coils visible, chiefly in umbilical region. Liver not felt. Splenic dulness definitely increased.

"The continued bacteræmia, the soft stools, abdominal distention, the facies and mental aspect of the patient, the distinctly enlarged spleen, all suggest a general infection which, but for the irregular fever, would be characteristic clinically of typhoid. The history, high leucocyte count and high blood urea and urinary findings point to a pyelonephritis."

The tachypnœa which was so striking on admission disappeared a few days later. The patient ran a prolonged irregular febrile course, 57 days elapsing before a normal temperature was maintained for 24 hours. Blood cultures were positive during most of this interval. (Rough quantitative determinations were made with the following results: On the 2d day of the disease about three colonies were present in each cubic centimeter of blood cultured; 22d day, two colonies per c. c. of blood; 26th day, two colonies per c. c. of blood; 33d day, one colony per c. c. of blood; 42d day, one colony in 10 c. c. of blood; on the 50th day, and thereafter, the blood was sterile on culture.) There were no chills nor sweats. During the first three weeks of his stay in the hospital the patient was occasionally found in a drowsy state, but was easily aroused and would answer questions relevantly. After the third week of his illness he became mentally clear and was bright and cheerful.

On November 29th (25th day of the disease) B. coli was isolated by culture from the bladder urine. This was interpreted as evidence of a secondary urinary invasion by the latter organism, B. paratyphosus B having been previously isolated in pure culture. A marked secondary anæmia developed, the red blood cell count and hæmoglobin reaching as low as 2,300,000 and 42%. Considerable variation in the leucocyte count was present.

On the 35th day of the disease the following note was made: "Perineal fistula is practically closed—pin-point in size—but still exudes a little pus. The patient is much less drowsy than previously, and feels well." The spleen was not felt.

Forty-sixth day: "Still running a moderate fever. Urine contains numbers of pus cells. B. paratyphosus B continuously in blood. He has developed a secondary anæmia and seems to have lost some weight. Otherwise the general condition is good .... Spleen not

felt." On this same day blood urea and blood CO_2 determinations were made and found normal.

Forty-eighth day: Cystoscopic examination revealed an œdematous, congested bladder mucosa, without other abnormalities. On ureteral catheterization urine containing pus cells and B. coli was obtained from both sides. From the left kidney urine atypical B. paratyphosus B was also isolated. The diagnosis of the urologist making the examination was "bilateral pyelitis."

After the 50th day the temperature became lower in the evenings, rarely reaching 100.5°, and on the 58th day it remained normal. The urine at this time showed only an occasional pus cell and a faint trace of albumin. With the exception of three sharp rises in temperature, each lasting only a few hours, the chart was not remarkable thereafter.

With the disappearance of the fever and gross evidence of urinary infection the patient's general condition rapidly improved. On February 9th the urine showed only an occasional white blood cell and a small amount of mucus. His color and nutrition were rapidly approaching normal, and he was discharged feeling entirely well except for slight weakness.

Discussion

The case is of considerable theoretical interest from a diagnostic standpoint. Was it an example of B. paratyphosus B pyelitis and septicæmia—a well-known clinical entity recognized and described by Schottmüller,* or were we dealing with a paratyphoid pyelitis initiating a true paratyphoid fever by the production of a septicæmia? A third possibility (though it is highly improbable in this case) is that the pyelitis developed as a complication of paratyphoid fever.

The third possibility hardly warrants discussion. The conclusion that the illness was initiated by the development of an acute pyelitis seems unavoidable from the history. Moreover, there is nothing in the history, or the examinations made in the wards previous to operation, suggestive of pre-existing paratyphoid fever. We come then to a consideration of the other two possibilities.

Was there a focal infection (pyelitis) with B. paratyphosus B which, by the continuous "breaking over" into the blood stream by the organism, finally brought about the more common generalized infection (paratyphoid fever)? We have not been able to find a proven case of such an occurrence in the literature. In his comprehensive review of the subject Schottmüller makes no mention of its occurrence. In our case the clinical evidence seems for the most part to be against this possibility. The classical typhoidal state was not constantly present. The spleen, though somewhat enlarged later in the disease, was never palpable and there were no rose spots. The temperature and pulse chart was essentially septic in type. Moreover, the absence of a leukopœnia with relative lymphocytosis is suggestive, though by no means conclusive, in the presence of a definite urinary infection. An intermittent diarrhœa was present but repeated examinations of the stools for B. paratyphosus B were negative. The prolonged septicæmia (the last positive blood culture was obtained on the 42d day of the disease) would seem to support this hypothesis to some extent—although the blood, as a rule, in paratyphoid fever becomes sterile after the third week.

* Schottmüller: Handb. d. inner. med., v. Mohr u. Staehelin.

We come then to the conclusion that the case is one of cystopyelitis of B. paratyphosus B origin, the most unusual feature of the condition being the prolonged septicæmia. The bacteræmia in itself is not unusual. It disappears as a rule, however, in from eight to twenty-one days. Moreover, in our case the rough quantitative determinations of the number of organisms in the blood stream at different stages of the disease are somewhat more suggestive of a general infection than of focal infection with incidental septicæmia. However, in the absence of other clinical and laboratory evidence of this condition (particularly the persistent absence of organisms in the stools) we do not feel that a diagnosis of paratyphoid fever is justifiable.

Historical Review of the Salmonella Group of Organisms

The etiological agent of the disease which has been reported above falls into the Salmonella group of bacteria, and it may not be amiss to review briefly the important features of this group with special reference to classification—in so far as it is possible to classify its members with the knowledge at hand.

By definition (Castellani) this genus is comprised of organisms which grow well on ordinary laboratory media; do not form endospores; are aërobes and often facultative anaërobes; without fluorescence, pigment formation or gelatin liquefaction; are without polar staining; are Gram-negative without a capsule; completely ferment glucose but do not ferment lactose; partially or completely ferment manitol, in addition to other carbohydrates. Milk is not coagulated.

The organisms falling under the above definition have been isolated for the most part during the past 25 years. The group has been extensively studied and its members classified on one basis or another, but as to their exact place within the group, and their relation one to another, relatively little is known.

In 1888 Gärtner [1] described a bacillus (B. enteritidis) isolated from beef which had caused a small epidemic of meat poisoning. The organism was found in the blood and spleen of a patient dying of the disease. Similar epidemics were described by Van Ermengem,[2] Holst,[3] Basenau [4] and others. De Nobele [5] in Belgium and Durham [6] in England described organisms giving rise to epidemics of gastroenteritis among groups of people in their respective countries. As a result of these more or less independent reports, a number of names for what is probably one and the same organism have been introduced into the literature. It is generally believed now that Gärtner's B. enteritidis, Basenau's B. bovis morbificans, B. morselle of van Ermengem, B. aertrycke of De Nobele and the organisms isolated and described by workers in similar epidemics are practically identical culturally and serologically—and some authorities feel that the name B. enteritidis (Gärtner) should be used exclusively for their designation.

In 1895 Gilbert [7] introduced the name "paracolon" to be applied to organisms occupying an intermediate place between the known typhoid and colon groups. In 1896 Achard and Bensaude [8] isolated from the urine of a patient with clini-

cally enteric fever an organism which they called a "paratyphoid" bacillus. Gwynn[9] in 1898 isolated a bacillus from an individual presenting the symptoms of typhoid fever, with cultural characteristics similar to those of B. enteritidis and which he called a "paracolon" bacillus. The patient's serum contained agglutinins for this organism but not for B. typhosus. A similar organism was isolated by Cushing[10] in 1900 from a costochondral abscess which had occurred during a "typhoid" convalescence. (The patient was said to have had a severe, though typical, attack of typhoid fever by her attending physician.) Cushing made an extensive study of the organism and concluded that it was an intermediate between B. typhosus and the colon group. In 1900 Schottmüller[11] obtained from five enteric patients organisms similar culturally to those of Achard and Bensaude, Gwynn and Cushing. By careful cultural and serological studies Schottmüller, Brion and Kayser showed that there were two distinct types present—one resembling the typhoid type (Paratyphosus A) the other resembling the enteritidis type (Paratyphosus B). Confirmatory findings were soon reported by other observers.

Other members of this group should be mentioned for the sake of completeness, and in order that a comprehensive view of the genus Salmonella may be obtained—B. suipestifer of T. Smith, B. typhi murium of Loeffler, B. icteroides of Sanarelli, B. psittacosis of Nocard and B. danysz.

Seiffert[12] in 1909, and Bainbridge[13] in 1910, considered the paratyphoid and allied organisms as a group. The latter concluded that the following classification could be made on cultural and serological grounds.

Salmonella group
1. B. paratyphosus A.
2. B. paratyphosus B.
3. B. enteritidis (Gärtner).
4. B. suipestifer.

He (Bainbridge) felt that B. psittacosis, B. typhi murium, B. morbificans bovis, B. icteroides, B. danysz, and other organisms commonly placed in this group, are all identical with one or another of the four organisms listed above, or mixtures of them. He considered B. enteritidis (Gärtner) as identical with B. danysz, B. aertrycke and B. morbificans bovis; B. typhi murium as identical with B. suipestifer or B. enteritidis, or an admixture of B. enteritidis and B. suipestifer; B. psittacosis as identical with B. suipestifer.

PARATYPHOID "C"

Bainbridge, in the discussion mentioned above, referred to a paratyphoid organism called "A" which, he stated, did not give the specific serum reactions with antiparatyphoid sera and which was antigenically different. It apparently did not fall into any of the groups discussed by him in his classification of the genus Salmonellæ. Zupnik[14] working with the organisms isolated by Cushing and Longcope in this country concluded that they belonged to a group different from either Paratyphosus A or Paratyphosus B. Messerschmitt[15] refers to an organism culturally a member of the paratyphoid group but which is different serologically from either B. paratyphosus A or B. In 1913 Uhlenhuth and Heubner[16] reported strains of organisms isolated from cases of hog cholera and from human feces which were similar to the paratyphoid organisms culturally, but which were inagglutinable in both anti-paratyphoid and anti-enteritidis sera. These organisms they called B. paratyphosus "C."

Since 1913 a number of writers have called attention to members of this paratyphoid-enteritidis group and a considerable literature has resulted. Particularly during the world war did these organisms come into prominence. In 1916 Hirschfeld,[17] chief bacteriologist for the Serbian Army, isolated an organism from the blood of a soldier who was thought to be suffering from paratyphoid fever. However, the organism was found to be serologically different from both B. paratyphosus A and B. Hirschfeld was able to recover, in all, 18 such organisms by blood culture from as many patients. He regarded it as a "new germ of paratyphoid fever" and called it B. paratyphosus "C." It was incorporated into the polyvalent antityphoid vaccine used by the Serbian Army. Working with a strain of Hirschfeld's B. paratyphosus "C," Dudgeon and Urquhart[18] prepared an antiserum which agglutinated the homologous organisms in dilutions of 1-20,000, but which did not agglutinate either B. typhosus, B. paratyphosus A or B. paratyphosus B. They absorbed this serum with all three of the latter named organisms (*i. e.*, B. typhosus, B. paratyphosus A, and B. paratyphosus B) and found that none of the homologous agglutinins were removed. However, they concluded that some paratyphoid "C" antigens have a definite paratyphoid B fraction. Castellani[19] in 1916 reported the recovery of six strains from enteric infections in the Adriatic-Balkan area which were similar culturally to the paratyphoid organisms but which were serologically distinct from them. Archibald, Hadfield, Logan and Campbell,[20] in 1916, reported similar findings at the Dardanelles. MacAdam[21] described a series of inagglutinable organisms isolated in Bagdad in 1918, morphologically and culturally indistinguishable from B. paratyphosus B, but serologically different. This worker concluded from serological studies that he was dealing with an organism distinguishable from both B. paratyphosus A and B, but closely related to B. paratyphosus B and B. aertrycke. Mackie and Bowen,[22] also working in Bagdad, report studies of several strains of organisms obtained by blood cultures from patients presenting, in the main, symptoms of the enteric group of diseases. From this work and observations subsequently made at the Lister Institute it is almost certain that they were dealing with organisms indistinguishable from Hirschfeld's B. paratyphosus "C." Kennedy[23] reports from India the isolation of five strains of an organism differing from both B. paratyphosus A and B, and probably identical with Hirschfeld's organism. Patton[24] records four strains of inagglutinable paratyphosus B in Egypt. No absorption tests are reported. Garrow[25] describes a strain from South Africa which was later found by Ledingham to be identical with Hirschfeld's. Broughton-Alcock[26] isolated by blood culture an organism differing from B. paratyphosus B in that it was non-motile and fermented dulcite only after repeated sub-

cultures. Serologically it reacted with B. paratyphosus B, and by absorption tests it was found to differ from B. aertrycke and B. gärtner. Dean [27] reports five strains from dysentery cases in Australia which apparently are quite similar to Hirschfeld's organism.

It is obvious that most of the reports cited above are from workers behind the Allied lines. It is interesting to note that German bacteriologists also met with atypical organisms which obviously belong to the group under discussion. Neukirch and Weil, in 1915, isolated an organism in Constantinople which they called B. ersindian. Culturally it resembled in all respects B. paratyphosus B, but proved to be definitely different serologically. It occurred in dysenteries. Weil later isolated it in Albania from patients without dysentery but presenting symptoms of sepsis. Dienes and Wagner reported similar cases from Eastern Europe. Levy and Schiff [28] saw 80 cases of this infection in Turkey and Palestine. In their article they recall Neukirch's classification of these infections into (1) septic, (2) typhoidal, and (3) dysenteric groups, and on account of the varying clinical pictures presented by the patients they raise the question as to whether or not the presence of the bacillus in the blood stream is not an accidental finding, just as B. suipestifer is in hog cholera.

In 1917 Weiss and Rice [29] reported the recovery of 15 strains of so-called B. paratyphosus C in this country and suggested that infection by it is more common than is generally recognized. In reviewing the literature we have met with no other reports of this group of organisms from workers in the United States.

Cultural Characteristics of the Paratyphoid Group

Culturally, B. paratyphosus A differs in but few respects from B. paratyphosus B. The former usually grows scantily on potato while with the latter the growth is abundant. B. paratyphosus B in litmus milk produces a primary acidity which rapidly changes to an alkaline reaction, as contrasted with the prolonged acidity of B. paratyphosus A. Krumweide, Pratt and Kohn [30] found that, while for the most part this statement holds, a moderate number of A and B types give intermediate reactions, so that the two groups merge. Jordon [31] concludes that this difference between the para A and B types in rapidity of alkalinization of milk is largely, if not altogether, a numerical relation due to gradations in the amount and rate of multiplication of the organisms. Burnet and Weissenbach [32] note that B. paratyphosus B reduces lead acetate (H_2S production), causing a darkening of the agar to which it has been added, thus differentiating it from B. paratyphosus A. Krumweide, Pratt and Kohn [33] found that 50 paratyphosus A strains and 14 paratyphosus B strains were sharply differentiated by the reduction and non-reduction of fuchsin from glucose-serum-water media. (Paratyphosus A caused reduction and Paratyphosus B caused no reduction.) These same observers [34] found that with their strains, which were agglutinatively A, xylose fermentation did not occur.

From the above review of the cultural differences of two fairly fixed types as B. paratyphosus A and B, it would be surprising indeed to find that organisms, so closely allied to B. paratyphosus B as members of the so-called C group, possessed distinctive cultural characteristics; and as a matter of fact they do not. No mention is made in the literature of the existence of any cultural differences between B. paratyphosus B and this recently described group, with one exception. Weiss and Rice [29] noted that none of their 15 strains produced gas on inosite, whereas, of 25 strains of B. paratyphosus B, 19 produced gas within 18 hours, while 6 produced no gas at the end of 6 days. The organism recovered from our case does not ferment inosite.

Serological Characteristics of the Group

It is evident from the discussion of the cultural characters of the paratyphoid group that differentiation of its members on that basis is uncertain. Serological methods are employed, and it was by the use of these methods (specific antisera and Castellani's agglutinin-absorption test) that the investigators cited above were led to believe that in the so-called B. paratyphosus C they were dealing with a third form of paratyphoid organism. However, their results varied considerably. Some strains were altogether inagglutinable by specific agglutinating serum for B. typhosus, B. paratyphosus A, B. paratyphosus B and B. enteritidis, but agglutinated in high dilutions of serum prepared by the use of so-called paratyphosus C antigens. Other strains reported were agglutinated by one or more of these specific antisera, but only in high concentrations. By the use of the agglutinin-absorption test in practically every instance it was shown that this agglutination was due to the presence in the sera used of co-agglutinins, and that absorption of the latter with the bacillus under investigation (B. paratyphosus C) did not alter the serum's agglutination-titer for its homologous organism.

The fact that the organisms reported show considerable variations to specific sera, together with the fact that on animal inoculation many strains produce, in considerable concentration, co-agglutinins for allied groups of organisms, while others do not, suggests immediately the possibility that we are not dealing with a single organism representing a new type but with a group of organisms, closely related to one another. Since all of the strains reported are allied to B. paratyphosus B, it is not improbable that the so-called paratyphosus C group represents variants of B. paratyphosus B, some being almost identical with the mother-type, while at the other extreme B. enteritidis is approached. Schutze [35] working at the Lister Institute made a critical study of the entire paratyphoid group with agglutinin-absorption tests. In this work he dealt with many of the strains referred to above. He concluded, on the basis of his findings, that the Hirschfeld strain is a true member of the paratyphoid B group, and that the term "paratyphoid C" should not be used in connection with it and similar organisms. He insists that the latter term was introduced into the literature by Uhlenhuth

to designate an organism which had "no agglutinogenic relationship, active or passive, to B. paratyphosus B and that, while some members of the Hirschfeld series may be entirely inagglutinable by para B sera, "others do respond to a greater or less extent, and all give sera which agglutinate B. paratyphosus B to a considerable degree." (Although Schutze did not work with any of the strains isolated by German workers, the description of the organisms isolated by the latter, as well as the proximity of the places of isolation, make it quite clear that the British and German workers were dealing with similar or closely allied infections. It would therefore seem highly probable that these strains would also fall into Schutze's large paratyphosus B group.)

DESCRIPTION OF THE ORGANISM

The organism isolated in the case reported in this paper was first recovered in blood culture November 3, 1920. It proved to be a Gram-negative, mobile bacillus and a prolific grower on the ordinary laboratory media. Litmus milk was first acidified (24 hrs.) and then immediately alkalinized (48 hrs.). Its action on the various sugars is as follows:

Glucose Levulose Mannite Galactose	Acid and gas.	Saccharose Lactose Inulin Raffinose Inosite Dulcite	No acid. No gas.

There is no production of indol. Media containing lead acetate are darkened within 24 hours. Gentian violet[20] (1-10,000) does not inhibit its growth. Glucose-serum-water is turned light pink color and a scant, fine precipitate occurs.

Culturally, then, we found that we were dealing with an organism of the paratyphoid group, and probably of the B. paratyphosus B division.

Serologically its identity was uncertain. With the first antiparatyphoid sera used we recorded the following results:

"H L" Antiparatyphosus A serum: No agglutination.

"H L" Antiparatyphosus B serum: Agglutination 1-150.

At this time the patient's serum agglutinated a killed culture of B. paratyphosus B in dilutions of 1:50. There was no agglutination with B. paratyphosus A.

TABLE I

	Before absorption	After absorption with Bacillus "X"
"A. T." Serum* v. B. paratyphosus B (N. Y.)	Agglutination 1-2,500	Agglutination 1-2,500
	Before absorption	**After absorption with B. paratyphosus B (N. Y.)**
"A. T." Serum v. Bacillus "X"	Agglutination 1-1,000	No agglutination

*A polyvalent antityphoid serum containing agglutinins for B. typhosus, B. paratyphosus A and B. paratyphosus B.

The low titer of our antiparatyphosus B serum against the unknown, together with the knowledge of the fact that organisms apparently falling into the paratyphosus B group are notoriously deceptive as to their identity, indicated the necessity of employing other methods for its identification. Castellani's absorption method was used. For purposes of simplification the organism under discussion will be called Bacillus "X" throughout the remainder of this report.

Thus it was shown that Bacillus "X," while agglutinated by the specific paratyphosus B fraction of the "A. T." serum used, was unable to remove the paratyphosus B agglutinins from the serum.

To confirm the above findings similar tests were made with two different monovalent antiparatyphosus B sera, with the following results:

TABLE II.—ANTIPARATYPHOSUS B SERUM NO. 684

	Before absorption	After absorption with Bacillus "X"
Serum No. 684 v. B. paratyphosus B (N. Y.)	Agglutination 1-1,280	Agglutination 1-1,280
	Before absorption	**After absorption with Bacillus "X"**
Serum No. 684 v. Bacillus "X"	Agglutination 1-1,280	No agglutination

TABLE III.—ANTIPARATYPHOSUS B SERUM NO. 999

	Before absorption	After absorption with Bacillus "X"
Serum No. 999 v. B. paratyphosus B (N. Y.)	Agglutination 1-2,560	Agglutination 1-2,560
	Before absorption	**After absorption with B. paratyphosus B (N. Y.)**
Serum No. 999 v. Bacillus "X"	Agglutination 1-1,280	No agglutination

(In each of the experiments detailed above, and in those which are to follow, a salt and serum control was run to reveal "spontaneous agglutination" if present. Absorption was proved to be complete in each case before the cross-agglutination tests were run.)

From the above protocols it is evident that the same phenomenon met with in the use of the "A. T." serum is also present when the monovalent paratyphosus B sera are used, that is to say, Bacillus "X" is unable to absorb out the specific paratyphosus B agglutinins from the sera, while B. paratyphosus B constantly absorbs out the co-agglutinins present in the sera for Bacillus "X." Nevertheless, in considering the results of these experiments, it is noteworthy that Bacillus "X" is agglutinated almost to the full titer of the serum for B. paratyphosus B.

To investigate further the validity of the assumption of the presence of co-agglutinins in the above sera as the explanation of the agglutination of Bacillus "X" by them, and also to

study the antigenic properties of the organism the following absorption experiments were made with the patient's serum:

TABLE IV

Patient's serum *v.* B. paratyphosus B (N. Y.)	Before absorption	After absorption with Bacillus "X" (homologous organism)
	Agglutination 1–160	No agglutination
Patient's serum *v.* Bacillus "X" (homologous organism)	Before absorption	After absorption with B. paratyphosus B (N. Y.)
	Agglutination 1–320	Agglutination 1–80

The above experiment was repeated, another strain of B. paratyphosus B (Sch. of H.) being employed, with similar results. Careful controls were run to guard against misinterpretation through "spontaneous agglutination" and incomplete absorption.

From the above experiment it would seem that we are dealing with two organisms antigenically different. (In spite of the low titer of the patient's serum we believe it permissible to utilize his serum as one showing specific immunity [agglutinins] for the organism being studied.) Here, too, the phenomenon of group agglutination is quite apparent.

Similar experiments were performed with the patient's serum and B. enteritidis (Gärtner) and B. suipestifer. The latter organism showed no agglutination whatever. The protocol of the former experiment is given:

TABLE V

Patient's serum *v.* B. enteriditis	Before absorption	After absorption with Bacillus "X" (homologous organism)
	Agglutination 1–160 (*atypical)	No agglutination
Patient's serum *v.* Bacillus "X"	Before absorption	After absorption with B. enteritidis
	Agglutination 1–320	Agglutination 1–320

* These tubes showed a finely granular appearance instead of a flocculent precipitate as in the case of Bacillus "X."

Substituting two known antiparatyphosus B sera for the patient's serum the above experiment was repeated with B. enteritidis. (B. suipestifer was not agglutinated by either of the antiparatyphosus B sera used.) The results in each case indicated clearly that the agglutinins present in these sera for B. enteritidis were group agglutinins, and that their removal had no appreciable effect on the agglutination titer of the sera for B. paratyphosus B. Moreover, they were removed when the sera were absorbed by B. paratyphosus B.

In order to study further the antigenic and serological characteristics of this organism a normal rabbit was immunized by the intravenous introduction of graduated doses of a killed broth culture of Bacillus "X," resuspended in salt solution. The immunization resulted in a serum which agglutinated the homologous organism in dilutions of 1-2400. At the same time a second rabbit was immunized to our stock strain of B. paratyphosus B (N. Y.). The second serum has a titer for the homologous organism of macroscopic agglutination in dilutions of 1-2400.

As in the above experiments agglutination, cross-agglutination and absorption tests were performed. The tabulated results follow:

TABLE VI

	Bacillus "X" immune serum	B. paratyphosus B immune serum
B. paratyphosus B.....	Aggt. 1–640	Agglutination 1–2,560
Bacillus "X".....	Aggt. 1–2,560 ..	Agglutination 1–160
B. suipestifer.....	Aggt. 1–320	
B. enteriditis.....	Aggt. 1–160	

The Bacillus "X" produced in the rabbit's serum, as in that of the patient infected, agglutinins for closely allied organisms. The absorption-tests which follow (Tables VII, VIII and IX) indicate that, as in the other serum, these are co-agglutinins the removal of which, by absorption of the serum with these organisms, has no effect on the titer for the homologous strain.

TABLE VII

Bacillus "X" antiserum *v.* Bacillus "X"	Before absorption	After absorption with B. paratyphosus B (N. Y.)
	Agglutination 1–2,560	Agglutination 1–1,600+
Bacillus "X" antiserum *v.* B. paratyphosus B (N. Y.)	Before absorption	After absorption with Bacillus "X"
	Agglutination 1–640	No agglutination

TABLE VIII

Bacillus "X" antiserum *v.* Bacillus "X"	Before absorption	After absorption with B. suipestifer
	Agglutination 1–2,560	Agglutination 1–1,600+
Bacillus "X" antiserum *v.* B. suipestifer	Before absorption	After absorption with Bacillus "X"
	Agglutination 1–320	No agglutination

TABLE IX

Bacillus "X" antiserum *v.* Bacillus "X"	Before absorption	After absorption with B. enteritidis
	Agglutination 1–2,560	Agglutination 1–1,600+
Bacillus "X" antiserum *v.* B. enteriditis	Before absorption	After absorption with Bacillus "X"
	Agglutination 1–160	No agglutination

A similar absorption experiment was performed with the antiparatyphosus B (N. Y.) serum,

TABLE X

Antiparatyphosus B (N. Y.) serum *v.* B. paratyphosus B (N. Y.)	Before absorption	After absorption with Bacillus "X"
	Agglutination 1–2,560	Agglutination 1–2,560
Antiparatyphosus B (N. Y.) serum *v.* Bacillus "X"	Before absorption	After absorption with paratyphosus B (N. Y.)
	Agglutination 1–160	No agglutination

Here also it is obvious that the organisms are antigenically different.

SUMMARY

(1) An organism was isolated from the blood of a patient who initiated his general infection by the development of a cystopyelitis (the latter following urethral stricture). A bacteræmia persisted over six weeks. A septic fever was present with leucocytosis. The organism was recovered on numerous occasions from the urine and blood, but never from the stool. With the cure of the urethral stricture and the subsidence of the cystitis and pyelitis the bacteræmia disappeared and the patient apparently made a complete recovery. The condition is an example of a clinical entity infrequently encountered but fully described by Schottmüller.

(2) The organism morphologically and culturally corresponds to B. paratyphosus B, yet serologically and antigenically it shows marked differences from the stock strains of B. paratyphosus B.

(3) It belongs to a large group of organisms which has recently come into prominence as a cause of disease (particularly among soldiers), and whose geographical distribution has been limited for the most part to the eastern hemisphere. Members of this group have been called by those isolating them "B. paratyphosus C," "Inagglutinable B. paratyphosus B," "Paracolon Bacillus," etc., since they all show, to a more or less degree, definite serological differences from B. paratyphosus B. Some have been shown to differ antigenically from the latter organism.

(4) A number of these strains (all of those studied by Schutze[35]) give sera which agglutinate B. paratyphosus B to some extent. When considering the members of the group individually, one finds strains showing only slight differences, those showing moderate differences and those showing extreme differences from the accepted B. paratyphosus B.

CONCLUSIONS

(1) The organism described in this communication is a member of the group which has rather loosely been called "paratyphosus C."

(2) Careful study has shown that this organism is closely related to B. paratyphosus B.

(3) It would not seem justifiable to employ the term "Paratyphosus C" in connection with this organism; it should rather be considered a variant of the B. paratyphosus B originally described by Schottmüller.

I wish to express my appreciation for the many valuable suggestions given me by Dr. A. R. Dochez, Chief of the Biological Division of the Medical Clinic of The Johns Hopkins Hospital and Medical School.

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GROWTH REQUIREMENTS OF INFLUENZA BACILLI

By T. M. Rivers and A. K. Poole

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Pfeiffer [1] discovered a new group of bacilli; he said that they were hemoglobinophilic and the cause of influenza. Since then much has been done to prove or disprove the various claims made for these bacilli by their discoverer. The controversy over the etiology of influenza will not be discussed here. Some, however, of the most significant work upon the hemoglobinophilic qualities of these bacilli will be cited and further evidence obtained in this laboratory bearing upon the subject will be submitted in this paper.

Grassberger [2] could not obtain a growth of influenza bacilli on media that contained hematin instead of hemoglobin except in symbiosis with other bacteria. Cantani [3] claimed he could grow them on media enriched with spermatic fluid which did not give the spectroscopic bands of hemoglobin. Ghon and Preyss [4] considered hemoglobin necessary even though it were present in such small quantities that it failed to give the bands with the spectroscope unless hydrazin were added. Nevertheless, they grew influenza bacilli on media containing hematin in symbiosis with other bacteria. Neisser [5] was able to grow influenza bacilli, isolated from a case of purulent conjunctivitis, on nutrient agar for 20 generations in symbiosis with a xerosis bacillus. Rivers [6] reported that he could grow both the hemolytic and non-hemolytic forms of these bacilli for a number of generations on hemoglobin-free media in symbiosis with other bacteria. Putnam and Gay [7] were unable to confirm Neisser's work. Davis [8] thought that hemoglobin acting as a catalytic agent was necessary for growth, and showed that a very small amount was required (1 part in 180,000 parts of medium). According to him, growth will take place in the presence of coagulated hemoglobin, but if the hemoglobin be broken up by excessive heating into hematin and globin no growth occurs. Fleming [9] was the first to offer proof that seriously interfered with the generally accepted idea, that hemoglobin is essential for the growth of influenza bacilli, by securing a good growth upon agar to which had been added a small quantity of fluid obtained by digesting blood with an equal amount of normal sulphuric acid and then neutralizing this with normal caustic soda. Olsen [10] obtained a growth of influenza bacilli on media containing hematin or hemin in symbiosis with other bacteria. Fildes [11] states that hemoglobin, unless changed, actually inhibits the growth of influenza bacilli and that there are two substances essential for the growth of these organisms. He is probably correct in saying that there are two factors, but his explanation based on the oxygen requirements of the bacilli is not necessarily true. Thjotta and Avery [12] consider two substances as essential for the growth of these bacilli. Both are in blood, one is resistent to excessive heating, the other is not. They do not think hemoglobin as hemoglobin to be one of the factors and also find the heat-labile substance in a number of bacteria and vegetables.

For several years to one of the authors (Rivers) the phenomenon of augmented growth of influenza bacilli in the vicinity of certain other bacteria under various conditions, called symbiosis, has been very interesting and seemed to hold in some way the secret of the real growth requirements of these bacilli. A study of this phenomenon of symbiosis has answered many questions and has shown that influenza bacilli are probably not hemoglobinophilic.

Augmented growth of influenza bacilli in the vicinity of other bacteria is more marked on human or hen blood agar plates than on rabbit, cat, dog or pigeon blood agar plates. In 1919 Rivers [13] showed that on 5 per cent fresh human blood agar a poor growth of influenza bacilli occurred, whereas on 5 per cent fresh rabbit or cat blood agar an abundant growth was obtained. An inhibitory substance, which did not exist in fresh rabbit serum, was found in fresh human serum, was removed by heating the serum for half an hour at 56° C., and was restored by adding a small quantity of fresh rabbit serum which in itself was not inhibitory. The phenomenon of symbiosis was marked on 5 per cent fresh human blood agar, whereas this was not true when rabbit or cat blood was used. The addition of the human blood to hot agar (95° C.) destroyed the inhibitory substance, allowing a splendid growth, and the picture of symbiosis sank into the background. Since then hen blood has been found to act similarly to human blood, while dog and pigeon bloods are like cat and rabbit bloods. The explanation for this phenomenon on fresh human blood agar and not on fresh rabbit blood agar was that the symbiotic bacteria removed in some way the inhibitory substance, just as heat does, allowing the influenza bacilli to grow best in their vicinity. This is only a partial explanation for the phenomenon as it occurs on blood agar and does not explain at all the fact that influenza bacilli can be grown on meat-infusion agar in symbiosis with other bacteria.

The change in hydrogen-ion concentration of the medium in the vicinity of the symbiotic bacteria next suggested itself as one of the factors entering into the picture observed on blood agar or meat-infusion agar plates. By some it is contended that this explains fully the augmented growth of influenza bacilli when grown with other organisms. To meat-infusion agar, pH 6.8, 7.6 and 8.6, was added 2.5 per cent fresh rabbit blood and 1 per cent glucose. Plates were made and inoculated with influenza bacilli. In the center of the plates, the three hydrogen-ion concentrations being used for each organism, were streaked *B. coli, B. alkaligenes,* and *Staphylococcus aureus.* The staphylococci and colon bacilli fermented the glucose and inhibited completely the growth of influenza bacilli near them on the plates with pH 6.8 and 7.6 (hydrogen-ion determinations were made before the blood was added). On the most alkaline plate, pH 8.6, the growth was best near the streak of colon bacilli, probably because of a

change in the hydrogen-ion concentration to a more favorable one for the growth of influenza bacilli. The opposite occurred on the plates streaked with *B. alkaligenes*. The growth of influenza bacilli was best near the streak of *B. alkaligenes* on the plates with pH 6.8 and a complete inhibition of growth occurred near the streak on the plate with pH 8.6. The blood near the center streaks was hemolysed and it could be seen that the hydrogen-ion concentration had been changed when the plates were flooded with brom-cresol purple. The striking thing, however, was that often just outside the zone of inhibition another zone of remarkably augmented growth occurred, reading thus: Streak of staphylococci near which would be no growth of influenza bacilli, then an unusually good growth, and then the usual growth on the plate at that hydrogen-ion concentration. Some of the phenomenal growth just beyond the zone of inhibition probably can be explained on the supposition that the hydrogen-ion concentration at that point and the action of the acid or alkali on the blood produce something more suitable for the use of influenza bacilli or liberate something in the process of breaking up the blood cells. This will be spoken of later.

Alkalies and acids were used for the center streaks to see if they would give the same results as bacteria. Blood agar plates of different hydrogen-ion concentrations were made as above and inoculated with influenza bacilli. Then acid or alkaline agar at 45° C. was placed on the center of the plates. Near these streaks the blood was hemolyzed or made brown and the same picture of inhibition and augmentation in the growth of the influenza bacilli was obtained as when bacteria were used, except that outside the zones of inhibition the areas of augmented growth, although present, were not so marked.

The fact that the zones of augmentation were more marked when bacteria were used suggested that they did not occur solely from an alteration in the blood, from the liberation of some substance in the blood cells, or from a change in the hydrogen-ion concentration, but in some way were influenced by the symbiotic bacteria. This is further confirmed by the fact that in growing influenza bacilli on meat-infusion agar in symbiosis with other bacteria the growth always occurred in the influenzal transplant nearest the symbiotic bacterial transplant. Sometimes the two transplants were half an inch to an inch apart. Whatever this substance may be, it is diffusible and reached the influenza bacilli by diffusion through the medium rather than by being carried to them by way of the air. This diffusible substance was considered one of the factors producing augmentation of growth of influenza bacilli near other bacteria and possibly a necessary factor for the growth of these bacilli under all conditions.

As it seemed possible that, in different bacteria or liberated by them in the process of growth, there is something which will augment the growth of influenza bacilli under various conditions, we added the extracts of bacteria to the media instead of making symbiotic cultures. Yeast was used first because it could be obtained easily in large quantities. One cake of bakers' yeast was mixed with 50 c. c. of distilled water, boiled one minute, filtered, and sterilized through a Mandler filter. To 100 c. c. of meat-infusion broth 15-20 c. c. of this yeast extract was added. This mixture was tubed in 10 c. c. quantities and was incubated to be sure of its sterility. When this medium was inoculated with influenza bacilli a good growth was obtained. The cultures were carried for 10 generations and discontinued. The first tube was inoculated with a loop of bacteria from a blood agar slant. Subsequent transplants were made by using 0.5 c. c. of the broth cultures. The bacilli in the tenth generation were growing normally, looked as usual under the microscope, formed indole, and were in pure culture when plated. When autoclaved yeast extract was used instead of that sterilized through a Mandler filter the medium was found unsuitable for the growth of influenza bacilli. The meat-infusion broth was made in the usual way and had been autoclaved 15 minutes under 15 pounds of pressure. These facts indicate that in yeast there is something essential for the growth of influenza bacilli and that it can be destroyed in the autoclave under 15 pounds of pressure for 15 minutes.

At this point the problem seemed an easy one, but soon it was observed that only certain lots of meat-infusion broth supported growth of influenza bacilli for many generations when the unautoclaved yeast extract was added. Another substance also appeared necessary for their growth and sometimes it was present in meat-infusion broth, at other times absent. Interest was fixed upon this second factor in attempts to find out what it was.

In looking over some experiments, several interesting facts were observed. Agar made with 2 per cent peptone and 0.5 per cent sodium chloride permitted growth of influenza bacilli only when more than 2.5 per cent fresh rabbit blood was added while the agar was at 45° C., and yet allowed a good growth when 0.5 per cent blood was added while the agar was 95° C. One drop of blood added to 100 c. c. of meat-infusion agar at 45° C. permitted little or no growth of the bacilli. If the agar were at 95° C. when the drop of blood was added a fairly good growth occurred. This was striking. So little blood, one drop in 100 c. c. of medium, certainly was not inhibitory because of some deleterious substance, inasmuch as 5 per cent of the same fresh blood with the same kind of agar allowed an abundant growth. Apparently in 5 per cent fresh unheated rabbit blood there was free enough growth-producing substances; while in one drop of unheated blood in 100 c. c. of agar not enough was supplied. Heating this one drop of blood to 95° C made available sufficient growth-producing substances. Others find that this alteration in the blood can be made with acids or pepsin as well as by heat.

The autoclave stable factor which at times was present in meat-infusion broth was sought for in blood. A clot from 500 c. c. of blood was infused with 200 c. c. of physiological saline solution, boiled, filtered, and autoclaved half an hour under 15 pounds of pressure. This autoclaved extract of blood clot was slightly brownish but did not give the spectroscopic bands of hemoglobin. An extract of yeast was prepared, half of which was sterilized through a Mandler filter, the other half in the autoclave. Two per cent peptone water

or agar was used as the basic medium. Influenza bacilli did not grow on these alone. If enough unheated rabbit blood, or "chocolate blood" were added, a good growth occurred. If 15-20 c. c. of the autoclaved blood clot extract, the filter-sterilized yeast extract, or the autoclaved yeast extract, were added alone to the peptone water or agar, no growth was obtained. If the autoclaved blood clot extract and the autoclaved yeast extract were added, there was no growth. If, however, the filter-sterilized yeast extract was used with the autoclaved blood clot extract, an abundant growth was secured for as many generations as desired.

When these facts are analysed, two substances at least are shown to be essential for the growth of influenza bacilli. Both of these are in blood; one resists autoclaving for 30 minutes under 15 pounds pressure, the other does not. The autoclave labile factor is found also in yeast. The autoclave stable one is not hemoglobin, if the spectroscopic examination or if autoclaving the blood clot extract half an hour be proof enough. So far this last factor has not been found outside of blood and may come from blood pigment even though it is not hemoglobin itself. In making media it has been noticed that some meats are bloodier than others. Certain lots of meat-infusion broth must contain enough of the autoclave stable substance from blood, as the growth of influenza bacilli is supported when unautoclaved sterile yeast extract is added. This explains the phenomenon of symbiosis on meat-infusion agar. The autoclave stable substance from the blood is in the agar and the autoclave labile factor is furnished by the symbiotic bacteria.

CONCLUSIONS

1. The phenomenon of augmented growth of influenza bacilli in the vicinity of other bacteria on solid media may be due to any one or, at times, all of the following factors:

(a) The removal of inhibitory substances that are marked in certain bloods, as human and hen's blood.

(b) The change of the hydrogen-ion concentration to one more favorable for the growth of influenza bacilli.

(c) The alteration in the blood, making growth substances more available.

(d) The production by the symbiotic bacteria of an autoclave labile substance necessary for the growth of influenza bacilli.

2. Two substances are essential for the growth of influenza bacilli. Both are in blood. One resists autoclaving half an hour under 15 pounds pressure, the other does not. The autoclave stable substance is not hemoglobin, although it may be derived from the blood pigment, and as yet has not been found outside of blood. The autoclave labile substance has been obtained also from yeast.

3. In what way these two factors operate to promote the growth of influenza bacilli is not known.

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THE GRADUAL WITHDRAWAL METHOD OF TREATING MORPHINISM: A MATHEMATICAL NOTE[1]

By JOHN RICE MINER

In the treatment of morphinism by gradual decrease of the dosage of morphine administered, a common procedure is to fill a bottle with distilled water to which is added a certain quantity of morphine. Enough of this mixture is administered as a first dose so that the morphine content will approximate the amount to which the patient has been accustomed. After removal of the dose it is replaced by an equal volume of distilled water. The second and subsequent doses are of

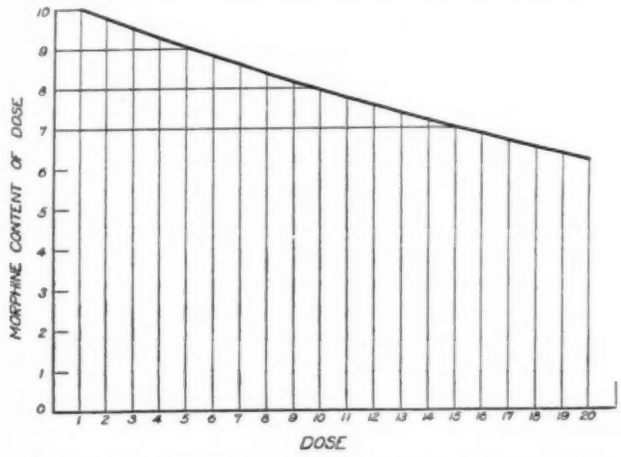

FIG. 1.—Morphine content of successive doses. The curve appears at first glance to be a straight line but it is really slightly convex to the base.

the same volume as the first, but as each time enough water is added to maintain the original volume of the mixture, the morphine content of the doses diminishes steadily. The question has been raised by one of the clinical departments of the hospital, as to the amount of morphine contained in the n^{th} dose, where n may have any value, as for example, 4, 5, or 10.

[1] Papers from the Statistical Department of The Johns Hopkins Hospital, No. 2.

Let there be originally M milligrams of morphine in solution in L c. c. of water, and let the one dose of the *solution* be $\frac{1}{k} \times L$ c. c. Let U_n represent the total amount of morphine present in the L c. c. of solution after $n-1$ doses have been taken out (*i. e.*, just before the n^{th} dose), and D_n the amount of morphine in the n^{th} dose.

$$D_i = \frac{U_i}{k}$$

since each dose is $\frac{1}{k}$ of the whole solution.

But

$$U_{i+1} = U_i - D_i = U_i\,(1 - \frac{1}{k}).$$

Therefore by mathematical induction, since

$$U_1 = M$$

$$U_2 = M(1 - \frac{1}{k})$$

$$U_3 = M(1 - \frac{1}{k})^2$$

.....

$$U_n = M(1 - \frac{1}{k})^{n-1}$$

For example, suppose $M = 400$ mg. of morphine, $L = 40$ c. c. and $\frac{1}{k} = \frac{1}{40}$, so that each dose is 1 c. c. in volume. Fig. 1 shows the morphine content of each dose from the first to the twentieth under these conditions.

At the tenth dose the morphine content is diminished by only one-fifth, and even at the twentieth dose by less than two-fifths. The decrease in dosage is much slower than might be supposed on first thought. A stage where the dosage of drug would be $\frac{1}{10}$ of the original dose would occur only at the 92d dose in the series. Incidentally it should be noted that the morphine would never entirely disappear from the bottle.

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THE FORMATION OF VACUOLES AND NEUTRAL RED GRANULES IN CONNECTIVE-TISSUE CELLS AND BLOOD CELLS OBSERVED UNDER ABNORMAL CONDITIONS

By Rosa E. Prigosen

(From the Carnegie Laboratory of Embryology, The Johns Hopkins Medical School)

Introduction

The accumulation in the cell of granules and vacuoles having a special affinity for neutral red is a phenomenon that has been studied in the living animal by Ehrlich (1894) in amphibia, by Metchnikoff (1907) in protozoa, by Fischel (1901) in the salamander, by Bethe (1909) in the rhizostoma, by Policard (1910) in the trypanosomes, by Coghill (1915) in the amphibian embryos, by Shipley (1916) in the trypanosomes, in the eggs of cerebratulus and in chick embryos by M. R. Lewis (1917, 1920), and by Clark and Clark (1918) in the tadpole. Numerous observers have also described these bodies in tissue cultures. Sundwall (1917), Matsumoto (1918) and Shipley (1919) used plasma cultures; Lewis and Lewis (1915), W. H. Lewis (1919), Hogue (1919), M. R. Lewis (1920), Smith (1920), and Matsumoto (1920) studied cultures in Locke-Lewis solution. Other investigators, describing the behavior of connective-tissue films (Renaut, 1907) and blood cells (Plato, 1900; Cowdry, 1914) have discussed certain neutral red bodies found in the cells. Cowdry, Gatenby, Duesberg, and others, in investigating the various structures of the cytoplasm, have incidentally referred to these granules. This work, initiated by Ehrlich and extended by numerous subsequent observers, has given rise to various theories and interpretations concerning the origin and functional activity of these granules and vacuoles.

At the suggestion of Prof. and Mrs. Lewis, a study of cells under abnormal conditions was undertaken in order to determine, if possible, whether altering the environment of the living cell in such a manner as ultimately to cause its death would affect the behavior of the cell toward neutral red and janus green.

Method and Material

Film preparations of subcutaneous connective tissue of 8- to 17-day chick embryos were made. The tissue covering the inguinal glands and legs yields the thinnest layer of fibroblasts and in the older chicks is of such a consistency that it can be easily manipulated on the slide. The piece of tissue, about 1 mm. square, excised from this region was carefully stretched upon a slide in a drop of plain Locke's solution, or in Locke's solution containing neutral red (1-10,000), and aerated for a few seconds before being flattened with a coverslip. Preparations in these two media were made at the same time. Some of each were sealed to exclude all oxygen. The preparations in Locke's solution were later stained with neutral red.

A film of connective tissue affords an opportunity for studying several kinds of cells—fibroblasts, clasmatocytes, and erythrocytes. The boundaries of the fibroblasts are not readily seen, but when defined are more or less spindle-shaped. These cells contain a few fat bodies and also mitochondria arranged somewhat radially at one side of the nucleus. The fat globules are highly refractive and can thus be distinguished from the subsequent degeneration products. The mitochondria, usually rod-shaped, occasionally assume a spherical or vesicular form, simulating somewhat the degeneration granules and vacuoles; from these structures, however, they can be differentiated by the use of the janus green or janus black.

Experiments

The experiments were grouped into seven series, each of which, with the exception of No. 6, was repeated many times. (1) Unsealed preparations of embryonic chick tissue in Locke's solution containing about 1-10,000 neutral red. (2) Sealed preparations of embryonic chick tissue in Locke's solution containing neutral red. (3) Unsealed preparations of connective tissue in plain Locke's solution. (4) Sealed preparations in Locke's solution. (5) Preparations of tissue from dead chick embryos. (6) Embryonic human blood in Locke's solution containing neutral red. (7) Adult human blood in neutral red solution.

Experimental Findings

All of the experiments, except in the dead tissue preparations, demonstrated the accumulation of neutral red granules and vacuoles in the cytoplasm of the fibroblasts during the degeneration stages of cytomorphosis. Microscopic examination revealed two distinct pictures, a negative, (*i. e.*, when no neutral red bodies were present) or nearly negative one, succeeded invariably by a positive phase (*i. e.*, by the presence of numerous neutral red bodies), becoming more pronounced as degeneration ensued.

Series 1.—The unsealed preparations in neutral red belong to a series of experiments in which none of the fibroblasts contained stained bodies when first examined—*i. e.*, within ten minutes after the application of the stain. After fifteen minutes a few scattered pink granules appeared in these cells and the tissue sometimes assumed a very faint pink coloration. These bodies rapidly increased in number, size, and intensity of color. From scarcely visible pink granules some of them became converted into angular, geometric forms of dark brick-red color, while others became larger in size and more rounded in outline, forming what are known as *vacuoles*. These bodies were paler and a more yellow-red than the granules. Frequently one or more of the brick-red granules

were found within the vacuoles, or in some instances the granules were surrounded by a pale yellow halo, which increased in size and became a vacuole. The granules ranged in size from scarcely visible specks to structures half a micron in diameter, while the vacuoles measured from five to ten times the diameter of the smallest granule. The cells remained alive and the neutral red bodies continued to accumulate in the cytoplasm for two hours or more. When the preparations were kept at a temperature of 39° C., there was actual propulsion of both granules and vacuoles through the cytoplasm. They appeared to travel along somewhat definite protoplasmic channels between the nucleus or the centrosphere and the more peripheral portion of the cytoplasm. The granules within the vacuoles exhibited Brownian movement.

The cytoplasmic arrangement of the granules and vacuoles was interesting and worthy of note. Their initial distribution was not constant; sometimes they were scattered uniformly throughout the cytoplasm, at other times they were gathered into clumps; again, the vacuoles and larger granules were grouped concentrically about the centrosphere and sparsely scattered at the periphery of the cytoplasm. Their final distribution, on the other hand, was strikingly characteristic, the granules and vacuoles being arranged about the centrosphere, as described by Lewis (1919).

Series 2.—In these sealed preparations, as in the unsealed, the granules and vacuoles appeared in about 20 to 30 minutes, increased in number and size but seemed to reach a maximum or standstill in about 45 minutes, the tissue dying shortly afterward.

Series 3 and 4.—The statements already made concerning the accumulation, size and arrangement of granules and vacuoles in the tissue prepared in solutions containing neutral red apply equally well to the cells of preparations in solutions without the dye. Except for a few highly refractive fat globules, mitochondria, and other granules, the cytoplasm of the fibroblast presented upon early examination a uniform appearance, which was later transmuted into a vacuolized structure having a lacy or frothy appearance. When Locke's solution containing neutral red was placed upon such a preparation, these vacuoles and granules immediately became stained in the same manner as did those which accumulated in the cells of the tissue placed directly in solutions containing neutral red, so that the two types of preparation could not be differentiated. The occurrence of vacuoles and granules in the unstained material is conclusive evidence that the phenomenon is not merely an accumulation of dye in the cell, but that there actually forms within the cytoplasm a structure which has a special affinity for neutral red.

Series 5.—The dead embryonic tissue in a solution of neutral red did not exhibit the intracellular accumulation of stained bodies but became diffusely colored, indicating that a marked change in the nature of the cell had taken place. Evans and Schulemann (1914) have demonstrated that dead tissue behaves quite differently from living cells, in that the benzidine dyes produce a uniform stain in dead cells. This may be due to a disintegration of the semi-permeable membrane, as McClendon and Mitchell (1911) have shown for other toxic substances. The uniform staining with neutral red is especially marked in tissue from embryos which have been dead for some time (undergoing autolysis) or in cell debris.

Tissue killed by fixation was found to behave quite differently. In some preparations the stain remained for some time, the results depending upon the dye employed and the fixing solution used. Lewis and Lewis (1915) stated that when the nile blue was used to stain cells which were later fixed, it disappeared from the vacuoles, and the mitochondria and fat globules then became stained. This did not occur in my observations when neutral red was used.

Dying cells showed all the transitions between the living cell and the cell debris. Contrary to the statement of MacCallum (1916, p. 53) that "a cell which had just died would look quite like its living neighbor," a moribund cell was easily distinguished from the living cells. The mitochondria became abnormal and disappeared; the cytoplasm became more fluid as was shown by the Brownian motion of the granules; and both cytoplasm and nucleus became slightly stained. Later the wall occasionally broke down and the cell became more deeply stained. At no stage in this degeneration did the neutral red leave the vacuoles to stain the mitochondria as claimed by Shipley, and when it did leave the stained bodies, the mitochondria had mostly disintegrated, and were therefore not present to become stained.

Series 6.—The blood of a human fœtus of six months, which I had an opportunity of examining through the courtesy of Dr. Shipley, did not exhibit any neutral red bodies except a few that developed in certain of the normoblasts.

Series 7.—A number of preparations of normal adult human blood were made in Locke's solution containing neutral red. When first examined, none of the blood cells except the eosinophiles contained any bodies stained with neutral red. The coarse granules, characteristic of these cells, stained at once a deep pink and later (within 10 to 40 minutes) the typical red vacuoles appeared (Fig. 5). Within 10 minutes after the application of the stain the specific granules of the polymorphonuclear leucocytes assumed a faint pink color. The vacuoles appeared within 15 to 30 minutes (Fig. 6) and were not unlike those in the fibroblasts and erythrocytes of the chick embryo. They were brick red and increased in size until much larger than those of the chick fibroblast. Vacuoles of different sizes also accumulated in the lymphocytes (Fig. 4), where they collected around the nucleus in such a way as partially to outline it.

The initial appearance of the vacuoles in the leucocytes was found to be partly dependent on the temperature at which the preparation is kept. When the blood smears were examined at 39° C. the vacuoles appeared earlier, the size increased more rapidly, and the bodies became larger than in those examined at room temperature. Movement of the vacuoles was more marked in the warm environment.

While the erythrocytes did not contain any neutral red bodies, when brilliant cresyl blue was used in the same manner as neutral red a blue body was observed in about 1 per cent of the cells.

In most of the preparations of chick material neutral red bodies were observed not only in the fibroblasts and clasmatocytes, but also in the erythrocytes (Fig. 3). In the last cells only vacuoles appeared. They were less numerous than in the fibroblasts, usually only one or two to a cell, although sometimes as many as ten were observed, in which case they outlined the nucleus. Stained vacuoles were observed in the erythrocytes of several preparations taken from a dead embryo in which the fibroblasts were apparently dead, as they stained diffusely.

The order of sequence in the development of the granules and vascuoles has not been conclusively determined. I am inclined to believe that in the fibroblasts the granular structure precedes the phenomenon of vacuolization, because in the tissues prepared in neutral red the granules are the first to appear. However, in the red blood cells and clasmatocytes of the chick, and in human white blood cells, as shown below, vacuoles appeared without being preceded by granules. This is contrary to the views held by Maximow (1916) and Shipley (1919), namely, that the vacuoles represent the final stage in the transition. In none of the preparations did the mitochondria become stained with neutral red, as has been claimed by Shipley (1915), Gatenby (1919) and others. The fact that in the eosinophiles the specific granules take the neutral red stain suggests the possibility that a neutral red granule may be normal in certain cells. In fact I have observed such granules in the amnion. These, however, were different in appearance and staining reaction from the bodies described above.

Discussion

The occurrence of bodies stained with neutral red, trypan blue, pyrrol blue, and other vital dyes, in the cytoplasm of the living cells has given rise to considerable discussion. Various theories have been formulated to explain the action of these stains; for example, the chemical theories proposed by Ehrlich and Overton and modified by subsequent investigators, and the physical, phagocytic theory advanced by Evans and Schulemann and supported by Clark and Clark, Matsumoto, Shipley and others. Then, too, diverse opinions have arisen concerning the nature of the granules, their relation to other cytoplasmic structures, and their physiological significance.

Action of the Stain.—The various theories regarding the action of the so-called vital dyes have been formulated largely by investigators who have used dyes other than janus green and neutral red. As my experiments were limited to these two stains, it is hardly practicable for me to discuss these theories at this time. However, in regard to the manner in which these dyes make their appearance in the cells, it seems to me that it is rather far-fetched to attempt to show a relation between this phenomenon and that of phagocytosis; for, regardless of how the stain makes its way into the cell, my experiments show that there is formed within the cell some bodies which have a special affinity for the dye—the mitochondria for the janus green and the granules and vacuoles for the neutral red. Without the presence of these bodies the dye does not become evident in the cell. It enters such a body and becomes accumulated therein in much stronger concentration than it was in the solution placed upon the cell.

Certain observers who have used neutral red have emphasized the fact that the death of the cell causes the neutral red to leave the stained bodies and appear as a diffuse stain in the cytoplasm. It is difficult to understand how the death of the cell could cause any ingested substance to leave a vacuole and become diffused through the cytoplasm unless it had been held in some chemical combination within the vacuole.

Nature of the Neutral Red Bodies.—Plato (1900), in conclusions drawn from experiments in which leucocytes were fed with red blood cells, dried white of egg, spermatozoa, and other cellular products, claimed that the bodies which appear in the cell under these conditions and which stain with neutral red are albuminous in nature. Galeotti (see Plato, 1900, p. 869) concluded that these bodies are food substances or secretion products. Cesa-Bianchi (1910) observed neutral red granules in the central half of the renal cells of the white mouse, and believed them to be liposomes because they stained with neutral red.

Albrecht (1903) found that liposomes of fresh muscle did not stain with neutral red, but that if kept aseptic at 37° C. in normal salt solution they took up the dye.

Bell (1911, p. 297) dissented from this view, as he did not succeed in staining any granules in muscle cells with neutral red. He stated: "In the kidney it is easy to show large numbers of neutral red granules. The number, size and arrangement of the granules show that they cannot correspond to the liposomes. The liposomes are not stained."

It has been suggested by McClenden and Mitchell (1911) that the neutral red bodies are lipoid in nature. According to them the egg is filled with lipoid particles which take neutral red. The view that they are lipoid in nature has not passed without opposition (Harvey, Aschoff and others). Aschoff (1910) found that none of the lipoid substances (lipochromes, neutral fats, free fatty acids, soaps, or cholesterin) stained with neutral red, except the myeline phosphatid (cerebroside) in autolysis. Harvey (1913) also questions the lipoid nature of the granules and states that the latter are probably lecithoproteid in nature. According to Mathews (1916), if an emulsion is made of lecithin or other phosphotide, egg albumen, and olive oil, it will be found that the granules of lecithin or phospholipin take up neutral red. Although he shows that other colloids of an electro-negative or anionic character stain in the same way, the behavior of some of the small granules of the cell in ether and when centrifuged seems to him to indicate that they are very much like lecithin.

Relation of Neutral Red Bodies to Mitochondria.—Cowdry[1] (1914), Lewis and Lewis (1915), Scott (1916), Sundwall (1917), M. R. Lewis (1917), and W. H. Lewis (1919), who

have used the double stain, have demonstrated that the mitochondria in connective-tissue and other cells stain with janus green in the presence of neutral red granules; and they have found no relation between the mitochondria and the neutral red bodies.

Duesberg (1911) mentioned various writers who claimed that certain vital dyes stain the mitochondria, but he himself doubted that neutral red and methylene blue possess this property.

Shipley (1915) first claimed that the mitochondria stain with neutral red, but later (1919) arrived at the conclusion that the mitochondria are not colored by neutral red but are specifically stained with janus green.

Gatenby (1918), in a communication on the cytoplasmic inclusions of the germ cell, stated that the mitochondria are stained *supra vitam* by janus green, neutral red, etc. Since it has been shown that neutral red does not stain the mitochondria, it is obvious that Gatenby was dealing with two types of granules, one of which takes neutral red, the other janus green, as was shown for the germ cells of the grasshopper by Lewis and Robertson (1916).

It appears to me that there are in general four distinct types of cytoplasmic granulations; the mitochondria, which stain with janus green; granules and vacuoles that stain with neutral red, the specific granulations normally present in the cell (for instance, the granules in the leucocytes and the eosinophiles); and fat globules that are not stained by either neutral red or janus green.

Physiological Significance of the Neutral Red Bodies.—In regard to the physiological significance of the neutral red bodies the observations given in the literature would seem to deal with three groups: (1) Structures which form in degenerating tissue, (2) digestive vacuoles, (3) bodies phagocytized by the cells.

Many of the investigators conclude that these bodies are abnormal or are an indication of the degeneration of the cells. W. H. Lewis (1919), in a detailed study of the significance of neutral red bodies in tissue culture of chick connective tissue, found that, as the cells grew old and degenerated, vacuoles and granules accumulated around the centrosphere. Both the vacuoles and granules became stained when a solution of neutral red was placed upon the culture. Owing to the fact that the accumulation of the granules and vacuoles was associated with the degeneration or approaching death of the culture, Dr. Lewis called the bodies degeneration vacuoles and granules.

Arnold (1899, p. 426) fed polymorphonucleated blood cells with neutral red. After a short time granules appeared. These soon exhibited variations in size and were sometimes inclosed in vacuoles. Referring to the vital staining of the tissues of plants and lower animals, Arnold states (p. 431) that the majority of authors have reached the conclusion that staining of cells takes place first when these cells begin to degenerate.

Minot (1912) described three ways in which the disintegration of erythrocytes of human embryos may take place: *i. e.*, by fragmentation, by bursting of the corpuscle, or by vacuolization; and he was perhaps the first to mention vacuoles in blood cells as an evidence of cell injury. Emmel (1914), who studied erythrocytes in the pig embryo, also considered the regressive and degenerative changes of the cells. He thought that the erythrocytes, taken from the circulation, must be in various stages of normal physiological degeneration and disintegration, and regarded the appearance of vacuoles in the cytoplasm as a degenerative change, a change which is most marked "in old cultures, homoplastic cultures, and in those experiments in which the plasma had been modified."

Cowdry (1914) observed, in the cytoplasm of finely granular leucocytes (neutrophiles), bodies that were stainable with both cresyl blue and neutral red. He stated: "It seemed clear that I was dealing with an accumulation of material resulting from the interaction of the stain and the cytoplasm, not with formed bodies preexistent in the living, unstained leucocytes." As claimed by Cowdry, the body which took the stain was not present in the normal cell, but neither was it caused by "the interaction of the stain and the cytoplasm." It is caused rather by an alteration of the cell itself during observation.

Lewis and Lewis (1915), in their observations on the mitochondria in tissue cultures, noted the formation of vacuoles during the degeneration of certain of the older cultures and attributed it to an excess of waste products accumulated around the cell.

Shipley (1916) noted the appearance of vacuole-like bodies which he thought were an "index of a degeneration change of some sort," because they were more numerous in trypanosomes which were losing their motility.

MacCallum (1918, p. 88) regarded the granules as degeneration products associated with pathological changes in the cell. The proteid nature of the granules occurring in the pathological condition known as "cloudy swelling" he seemed to consider as established, but he raised the question as to the origin of these granules and their relation to other structures of the cell.

Renaut (1907, p. 509), studying sealed preparations of the connective tissue of an adult rabbit in solutions of neutral red, found that the fibroblasts became full of vacuoles containing granules. In the embryonic connective tissue of sheep and cattle the appearance of the neutral red bodies was slower. They gradually developed, however, and were numerous at the end of half an hour. While Renaut did not perceive that they were abnormal, it seems to me quite probable that the neutral red bodies described by him, and also the so-called "liposomes" of Albrecht, are not normal structures of the cell but are comparable to those observed in my experiments, since the methods employed by these observers were sufficiently similar to my own to have produced abnormal structures.

Degeneration, as manifested by the appearance of vacuoles, has been frequently referred to in the literature; and, although in some cases neutral red was not used, it appears to me that certain of the structures observed are the same as the above described degeneration vacuoles which take the neutral red. Lillie (1908, p. 317) wrote: "Vacuolization of the tissue be-

tween the cloacal membrane and the urodæum indicates its subsequent disappearance."

Calkins (1909, p. 81) stated that, while numerous "gastric vacuoles are present in the normal and active paramecium, they disappear when starved, and that "great vacuoles" appear which increase in size with starvation.

Nickerson (1913), studying the intercellular canals in the skin of Phascolosoma, similarly noted the appearance of large vacuoles in old and degenerating cells, as well as differences in the staining properties of young and old cells.

On the other hand, a number of observers have claimed that the bodies which take the neutral red are not degeneration products but are digestive vacuoles. The distinction, however, should be easily made, since neutral red is itself an indicator (Harvey 1913), and many writers have asserted that the digestive vacuole is slightly acid (cerise red with neutral red). Metchnikoff (1907, p. 11) mentioned the presence of digestive vacuoles in the endoplasm of Paramecium and Infusoria in general, which feed upon numerous bacteria, and stated that the fluid content of these vacuoles has a "distinctly acid reaction," as demonstrated by the use of neutral red. Policard (1910) noted a difference between the brick-red degeneration vacuoles and the "cerise red" food vacuoles. Calkins, discussing the nature of the digestion processes in protozoa, emphasized the work of Englemann and Le Danteux, as well as that of Metchnikoff and others who showed acid reaction in gastric vacuoles of certain protozoa.

I have had occasion to observe amœbae stained with neutral red and have been immediately impressed with the decided rose tint of digestive vacuoles as compared with the yellow or brick-red color of those in my present observations. The fact that digestive vacuoles stain with neutral red may account for the discrepancies that have arisen concerning the functional activity of the degeneration vacuoles. Prowaczek (see Plato, 1900) was one of the first to deny that neutral red bodies in most cells were food vacuoles, and he believed them to be digestion granules or ferment bearers.

A number of writers have asserted that appearance of the neutral red bodies in the cell is related to the phenomenon of phagocytosis as described by earlier observers (Plato 1900, MacCallum 1903, Metchnikoff 1907). Plato claimed that the material which takes the stain is phagocytized by the cell. Clark and Clark (1918) and Matsumoto (1918) concluded that the dye itself may be phagocytized, while Shipley (1919) favored the theory of phagocytosis of substances which form the vacuoles, appear within a vacuole, or stain the vacuole. It seems to me hardly probable that cells in a simple salt solution such as Locke's solution, from which the oxygen was largely excluded, could have phagocytosed the material which formed the vacuoles and granules. On the other hand, the disturbed metabolism of these cells might result in the accumulation within the cytoplasm of substances which normally would have been eliminated.

Conclusions

1. Bodies having an affinity for neutral red accumulate in the cytoplasm of fibroblasts and erythrocytes of chick embryos when observed in film preparations.

2. Neutral red bodies are not present in dead tissue but are found in many kinds of degenerating cells.

3. The granules and vacuoles which appeared in cells studied in this manner were not due to the accumulation of dye in the cytoplasm nor to an interaction of the dye and the cytoplasm, but were the results of the abnormal condition of the cell.

4. The white cells of human blood observed in film preparations also developed vacuoles which stained with neutral red.

5. These bodies are probably not phagocytized by the cell nor do they correspond to the food vacuoles.

6. The behavior of the cells in film preparations in Locke's solution led to the conclusion that there are present certain bodies (the mitochondria) which stain with janus green but not with neutral red, and others, varying in number according to the condition of the cell, which stain with neutral red; also, that neither of these types arises from the other. In addition to these, there may be granules specific for a given type of cell, and also fat globules.

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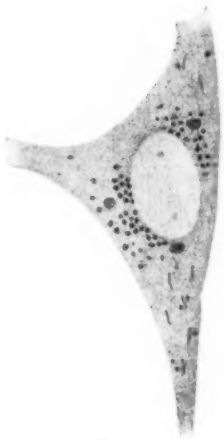

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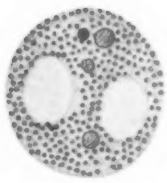

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DESCRIPTION OF PLATE

Camera lucida drawings showing the arrangement of neutral red granules and vacuoles, mitochondria and fat globules in various cells described in the text. Neutral red granules are shown as black dots; vacuoles as shaded circles; fat globules as black circles; and mitochondria as black rods and threads.

FIG. 1.—Fibroblast of a chick embryo showing neutral red granules and mitochondria.

FIG. 2.—Fibroblast of a chick embryo in which some of the granules are enclosed in vacuoles.

FIG. 3.—Erythrocyte of chick embryo containing vacuoles only.

FIG. 4.—Lymphocyte of adult human blood, exhibiting vacuoles and specific granules.

FIG. 5.—Eosinophile of adult human blood showing large vacuole and specific granules.

FIG. 6.—Neutrophile of adult human blood containing several vacuoles and specific granules.

NOTES ON NEW BOOKS

Gynecology. By BROOKE M. ANSPACH, M. D., with an Introduction by Dr. John G. Clark. Cloth, $9.00. (*Philadelphia and London: Lippincott Company, 1921.*)

The adequate presentation of even the essentials of gynecology, as it is practised to-day, within the confines of a single volume text-book is a task of no mean proportions. For not only does it involve a many-sided consideration of the female reproductive organs but also and necessarily of certain phases of abdominal surgery, of orthopedic surgery, of obstetrics, of urology, of internal medicine and of physico-therapy.

No one, however, who is familiar with Dr. Anspach's work as student, investigator, teacher and practical surgeon would question for a moment his ability to perform such a task with enviable efficiency. And when one finds the finished product dedicated to and sponsored by Dr. John G. Clark, who for years has so brilliantly adorned the Philadelphia clinic and whose name is synonymous with all of the best traditions of our profession, the inevitable mental reaction is one of pleasant anticipation rather than an attitude of critical fault-finding.

Moreover, a careful perusal of this book reveals that it has an intrinsic and substantial worth to recommend it quite aside from the happy circumstance of gifted parentage.

The opening chapters are devoted to an unusually lucid, concise, yet comprehensive adaptation to gynecology of the relevant matter from embryology, the developmental anomalies, anatomy and physiology. Next follows a series of chapters setting forth the details of history-taking and methods of examination, including not only the general physical as well as those special procedures available for investigating the pelvis and abdomen, but also the technique of a complete urologic study as well as that required for accurate inspection of the anus and rectum.

The diseases of each unit of the reproductive and urinary systems are then presented on an anatomical basis and discussed in a thoroughly satisfactory and logical manner.

In addition, the author has wisely incorporated a special chapter dealing with those diseases of the abdominal viscera so commonly associated with pelvic disorders and constantly requiring proper handling at the operating table.

Other special chapters are devoted to gonorrhœa, syphilis, and tuberculosis of the pelvic organs; one to the important subject of backache; one to menstrual disorders; and another to sterility.

While it was obviously impossible to incorporate in a work of this size all of the available operative procedures, yet admirable selective judgment has been used in the choice of those recommended, and in not a few instances the details of several are given.

Instructive and suggestive chapters are given on the preparation of the patient for operation, operative technique, post-operative management and complications.

Especially noteworthy are the chapters on hygiene of adolescence, mechano-, sero-, thermo-, and radio-therapy.

Appended to each chapter is a bibliography which includes references to all of the classic as well as the more important collateral contributions to the particular subject dealt with. This is a most excellent feature of the book and conspicuously reflects the author's familiarity with the literature as well as his painstaking care and judicious skill in estimating the work of others.

On the whole, the illustrations are excellent, the publisher's work has been well done and the index is adequate.

In a word, rarely has a text-book of this size been produced which possessed so many excellent qualities with so few deficiencies as does this one of Dr. Anspach. It reflects great credit upon the author and his associates and can be recommended without reservation to students and to the profession at large. E. H. R.

The Basis of Psychiatry. By ALBERT C. BUCKLEY, M. D. (*Philadelphia and London: J. B. Lippincott Company, 1920.*)

Buckley's book is an effort to adapt the psychiatric teachings of the Philadelphia School to the biological point of view. This shows, on the one hand, in the great amount of elementary biology and histology that is introduced and, on the other, in the acceptance of the concept of reaction-types, which leads to such an unusual and suggestive occurrence as the formation of a special chapter on the "præcox-manic problem." In the actual discussion of the psychiatric material the acceptance of a biological viewpoint is very much less in evidence. The psychology and psychiatry remain very much in the traditional garb and substance, with liberal rehearsal of the older psychiatry and the German additions of the late nineties, but very little contact with the later additions of American workers. The book is a means of handing on tradition and neither stimulating for actual investigation nor suggesting evidence of being based on material of experience worked out with psycho-biological and biological methods. It does, however, represent very truthfully a good average type of present-day practical psychiatry—conservative as to psychobiology, but willing to borrow analogies at least from the fundamental biological viewpoints. The real step towards a frank recasting of the psychiatric material and problems themselves on a psychobiological basis still remains to be taken. A. M.

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